EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA CHARLESTON DIVISION

IN RE: ETHICON, INC. PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LIGITATION	**Master File No. 2:12-MD-02327 MDL No. 2327**
THIS DOCUMENT RELATES TO PLAINTIFFS: **Huskey (2:12-cv-05201)** **Edwards (2:12-cv-09972)**	**JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

RULE 26 EXPERT REPORT OF BRUCE ROSENZWEIG, M.D.

I. QUALIFICATIONS.

I am currently an Assistant Professor of Obstetrics and Gynecology at Rush University Medical Center in Chicago, Illinois. I received my MD degree in 1984 from the University of Michigan in Ann Arbor, Michigan. Following graduation from medical school, I completed an Obstetrics and Gynecology Residency at Michael Reese Hospital in Chicago. In 1988, I attended a one year pelvic surgery fellowship at State University of New York in Syracuse, New York. Following that fellowship, I attended a two year Urogynecology and Urodynamics fellowship at UCLA Harbor General Hospital in Torrance, California. After graduating from the Urogynecology fellowship, I became a faculty member at the University of Illinois in Chicago. I started a Urogynecology program at the University of Illinois and also was the residency program director. In 1998, I went into private practice, and subsequently established a private practice at Rush University Medical Center. I have also worked at John H. Stroger Hospital here in Chicago from May 2003 until November 2010 and Weiss Memorial Hospital as Associate Chair of Gynecology from February 2011 until July 2012. I have published numerous articles

and given numerous lectures on the topics of pelvic organ prolapse, urinary incontinence and repair of pelvic organ prolapse.

Throughout my career, I have performed over a thousand pelvic floor surgical procedures, including abdominal sacrocolpopexy, uterosacral suspensions, sacrospinous ligament fixations, native tissue repairs, biological graft repairs and synthetic mesh repairs. I have also used numerous synthetic pelvic mesh products, including Ethicon's TVT, TVT-Obturator, and Prolift. In addition, I have performed over 200 surgeries dealing with complications related to synthetic mesh, including the removal of numerous TVT devices. I was also invited by Ethicon and attended both its Gynecare Prolift Training Seminar and TVT Obturator Seminar in Belgium. In addition, I was also invited and attended a Bard Avaulta training seminar.

A copy of my CV and Fee Schedule is attached as Exhibit "A" and a copy of my testimony for the last four years is attached as Exhibit "B". The documents I relied on for this report are contained in Exhibit "C" as well as those documents cited throughout this Report.

II. SUMMARY OF OPINIONS.

In formulating my opinions and preparing this report, I reviewed scientific literature, corporate documents from Ethicon, sample products and depositions of Ethicon employees. The corporate documents, sample products and depositions were supplied to me by counsel. A list of Ethicon corporate documents and depositions reviewed for this report is attached hereto as Exhibit "C"; all other materials reviewed are listed at the end of this report. All opinions I have are to a reasonable degree of medical and scientific certainty. I understand discovery is still ongoing in this case, and I reserve my right to amend my opinions if further information is provided in any form including, but not limited to corporate documents, depositions and the expert reports of both Plaintiff and Defense experts. In general, my expert opinions can be summarized as follows:

III. BACKGROUND AND TREATMENT OPTIONS FOR STRESS URINARY INCONTINENCE.

A. Stress Urinary Incontinence

Approximately one of three women over the age of 45 years old has some form of urinary incontinence. The majority of those women do not seek medical advice or treatment for a variety of reasons.

In a continent individual, increased abdominal pressure is evenly distributed over the bladder, bladder neck, and urethra. The urethral sphincter is thus able to withstand this pressure and maintain continence. In a person with pure stress urinary incontinence (SUI), either the urethra is hypermobile or the sphincter is intrinsically deficient. In urethral hypermobility, the urethrovesical junction (UVJ) is displaced extra-abdominally, and the increased intra-abdominal pressure is unevenly distributed such that the sphincter can no longer withstand the pressure and urine leaks. With intrinsic sphincter deficiency (ISD), the UVJ is not hypermobile; however, the maximal urethral closing pressure, the Valsalva leak-point pressure, or both are too low to withstand the increase in intra-abdominal pressure and, thus, urine leaks past the sphincter.

SUI is the involuntary leakage of urine during moments of physical activity that increases abdominal pressure, such as coughing, sneezing, laughing, or exercise, in the absence of a bladder contraction. It has been estimated that 14% of women have SUI. SUI is a common type of urinary incontinence in women. Urodynamic proven SUI is found in approximately 50 % of women presenting for evaluation of urinary incontinence. Symptomatic women with SUI have social or hygienic consequence from their urine loss. SUI can happen when pelvic tissues and muscles, which support the bladder and urethra, become weak and allow the bladder “neck” (where the bladder and urethra intersect) to descend during bursts of physical activity (urethral hypermobility). This descent can prevent the urethra from working properly to control the flow

of urine. SUI can also occur when the sphincter muscle that controls the urethra weakens (intrinsic sphincter deficiency). The weakened sphincter muscle is not able to stop the flow of urine under normal circumstances, and when there is an increase in abdominal pressure. Weakness may occur from pregnancy, childbirth, aging, or prior pelvic surgery. It has been estimated that a majority of incontinent women have a combination of urethral hypermobility and ISD. Other risk factors for SUI include chronic coughing or straining, constipation, obesity and smoking. Finally occult or latent SUI is defined as a positive stress test, loss of urine with increased intra-abdominal pressure and between 350-450cc volume in the bladder, after the repositioning of pelvic organ prolapse (usually accomplished with a ring pessary carefully positioned as to avoid compression of the urethra) in an otherwise clinically continent patient.

B. Nonsurgical Treatment of SUI.

There are numerous non-surgical treatments available to woman with SUI. First, Pelvic Floor Exercises: A type of exercise to strengthen the pelvic floor by contracting and relaxing the levator muscles that surround the opening of the urethra, vagina, and rectum. These exercises, commonly referred to as Kegel exercises, improve the pelvic floor muscles' strength and function. Kegel exercises can improve over-active bladders by increasing urethral resistance with can trigger the bladder to relax.

Second, Pessary: A removable device that is inserted into the vagina against the vaginal wall and urethra to support the bladder neck. This helps reposition the urethra to reduce SUI. These can be made of rubber, latex or silicon. Inserted into the vagina, a pessary rests against the back of the pubic bone and supports the bladder. Pessaries are available in various forms, including donut and cube shapes, and must be fitted by a healthcare provider. Some women who have stress incontinence use a pessary just during activities that are likely to cause urine leakage, such as jogging. Special incontinence pessaries have a 'knob', which fits under the urethra to

elevate the midurethra to prevent urine loss.

Third, Transurethral Bulking Agents: Bulking agent injections are applied around the urethra that make the space around the urethra thicker, thus helping to control urine leakage. The effects are usually not permanent.

Fourth, Behavioral Modification: This includes avoiding activities that trigger episodes of leaking. Lifestyle modification can improve stress incontinence symptoms and include quitting smoking, weight loss, and allergy treatment during seasonal allergies.

Fifth, Urinary seals: These are adhesive foam pads, which women place over the urethral opening. The pad creates a seal and prevents the leakage of urine, providing incontinence treatment. The pad is removed before urination and replaced with a new one afterward. The pad can be worn during exercise or physical activity, but not during sexual intercourse.

Sixth, Urethral insert: A thin, flexible tube that is solid rather than hollow (like a catheter) is placed into the urethra to block the leakage of urine. These small plugs are inserted into the urethra by women to prevent leakage, and are removed prior to urination. These inserts can be uncomfortable and may increase the risk of urinary tract infection.

Seventh, Bladder neck support device: This device is a flexible ring with two ridges. Once inserted into the vagina, the ridges press against the vaginal walls and support the urethra. By lifting the bladder neck, it provides better bladder control in women suffering from stress incontinence. The device needs to be sized to fit, and must be removed and cleaned after urination. Bladder neck support devices can be uncomfortable and may cause urinary tract infections.

C. Surgical Treatment of SUI.

1. <u>The Burch Colposuspension</u>.

Retropubic approaches for the treatment of stress urinary incontinence include the Burch

retropubic urethropexy (both open and laparoscopic) and the Marshall-Marchetti-Krantz (MMK) procedure. The goal of both of these procedures is to suspend and stabilize the urethra so that the urethrovesical junction (UVJ) and proximal urethra are replaced intra-abdominally and to recreate a firm backstop for intra-abdominal pressure. This anatomic placement allows normal pressure transmission during periods of increased intra-abdominal pressure restoring continence in a previously incontinent, hypermobile UVJ.

The Burch procedure was described in 1961. Initially, Burch described attaching the paravaginal fascia to the arcus tendineus. However, this was later changed to Cooper's ligaments because these were felt to provide more secure fixation points, and less chance of infection as seen with the prior MMK procedure.

Patients with type III stress urinary incontinence (a fixed, nonfunctioning proximal urethra) are not ideal candidates for a Burch procedure as no hypermobility exists to correct. For the Burch procedure, a low Pfannestiel incision is made above the pubic bone in order to enter the space of Retzius (the anatomical space between the pubic bone and the bladder above the peritonium in order to suspend the bladder and/or to perform a paravaginal repair. The procedure involves placing permanent stitches adjacent to the neck of the bladder and either proximal or distal to the bladder neck stitches on each side and suturing them Cooper's ligament which is attached to the pubic bone. The paravaginal repair is very similar except that the stitches are attached to the arcus tendentious linea pelvis. The likelihood of success of the Burch and the paravaginal repair procedures is reported to be 80-90% in most cases. Success means total elimination of the incontinence and patient satisfaction score greater than 90%. Improved means significant reduction of urine loss and greater than 70% improvement of patient satisfaction scores. Additionally, these retropubic procedures can be accomplished by the laparoscopic route.

With respect to the selection of synthetic absorbable suture versus non-absorbable suture, and braided versus monofilament, no prospective randomized blinded data exist to suggest superiority of one suture material over another. However, recognized risks are associated with bone anchors. Modifications in the technique can be used if co-existent central defect cystocele is present and obliteration of the cul-de-sac can be performed to prevent enterocele or posterior vaginal wall prolapse after Burch colposuspension.

2. Pubovaginal sling procedures.

Pubovaginal slings have excellent overall success and durable cure. The procedure involves placing a band of autologous, allograft, xenograft or synthetic material directly under the bladder neck (ie, proximal urethra) or mid-urethra, which acts as a physical support to prevent bladder neck and urethral descent during physical activity. This is brought up through the rectus fascia. The sling also may augment the resting urethral closure pressure with increases in intra-abdominal pressure.

Historically, surgeons have used the fascia lata sling for recurrent SUI after a failed anti-incontinence operation. Furthermore, this operation is used extensively for the treatment of primary ISD. If the abdominal tissues are weak and attenuated or if the vaginal tissues are atrophied or in short supply, constructing a pubovaginal sling from the leg fascia lata can be performed. This procedure is more involved than the creation of the rectus fascial sling as it requires a second incision to harvest the fascia lata and healing in an area remote for the index procedure.

An alternative to a long rectus sling is construction of a short sling from a much smaller piece of abdominal fascia (rectus fascia suburethral sling). The surgical procedure is similar to that used for the rectus fascia pubovaginal sling, except that the harvested fascial tissue is much smaller and the operation time shorter. The advantage of this procedure is its simplicity. No

extensive dissection in the suprapubic area is necessary, and the postoperative result is similar to that of the full-length fascial strip sling.

An alternative to a long fascia lata sling is the use of a postage stamp–sized patch of fascia lata from the outer thigh (fascia lata suburethral sling). The surgical procedure is similar to that for the fascia lata pubovaginal sling, except the harvested fascia is much smaller. This operation does not require extensive dissection in the thigh area, and the postoperative result is similar to that of the full-length fascia lata strip sling. Postoperative convalescence is shorter than that of the fascia lata pubovaginal sling procedure.

The vaginal wall suburethral sling helps restore urethral resistance by increasing urethral compression and improving mucosal coaptation of the bladder neck. This operation is attractive because it is simple and easy to perform. Postoperative complications are minimal, and the recuperative period is short. Vaginal sling surgery is relatively contraindicated in elderly women with atrophic vaginitis. If recognized before surgery, the atrophied vaginal wall may be revitalized with the administration of vaginal estrogen cream or tablets for 3-6 months.

A clear contraindication to pubovaginal sling surgery is pure urge incontinence or mixed urinary incontinence (MUI) in which urge is the predominant component. An inherent risk of any sling procedure is de novo or worsening urge symptoms; thus, surgeons must identify and treat the presence of an urge component before surgery.

Conversely, poor detrusor function is a relative contraindication to pubovaginal sling surgery because the potential for urinary retention is increased. Women with absent or poor detrusor function in the presence of SUI are at a higher risk of experiencing prolonged postoperative urinary retention.

3. <u>Midurethral Synthetic Slings</u>.

Based on the "Integral theory of female incontinence," Prof. Ulmsten developed a

midurethral procedure to treat stress urinary incontinence. The first reports of this procedure appeared in 1996 as an intravaginal slingoplasty. The "tape'" was place through a small vaginal incision at the midurethra, brought through the urogenital diaphragm through the retropubic space and exited through small suprapubic incisions. The operation was theorized to correct incontinence by recreating the midurethral support of the pubourethral ligament and also by creating a midurethral hammock for support of the urethra during stress events. The procedure was described to have a success rate of 85-90% with an additional 5-10% significantly improved. The Gynecare TVT system was introduced in the US in November of 1998. Early studies showed that the risk of bladder perforation during the procedure occurred 5-10% of cases and vascular injury with /without hematoma formation occurred in 2-5% of patients.

In an attempt to decrease the risk of bladder perforation and vascular injury, a 'top-down' approach to trocar placement was promoted as the SPARC procedure, introduced in the US in 2001 by American Medical Systems (AMS). The next modification of the midurethral sling came in 2001 when Delorme described his results for the use of the obturator membrane and inner thigh for passage of the sling material. The proposed advantage was avoidance of the retropubic space, thus avoiding bladder perforation and retropubic vascular injury. The trocars were passed from the inner thigh through the obturator membrane from an "outside – in direction".

The next modification came from de Leval in 2003, with the "inside-out" trocar placement for the transobturator sling. This device is the focus of this report. The final modification came around 2006 with the release of the mini-slings, or single incision slings, which use support devices at the ends of shorter mesh lengths to accomplish fixation without the need for a secondary cutaneous exit point. The mini-slings could be placed in a retropubic or

"U" fashion or a hammock or "H" fashion.

The FDA concluded in 2011 that there was higher peri-operative blood loss, higher mesh exposure and greater need for surgical re-intervention in the TVT-Secur (mini-sling) patients.

IV. EXPERT OPINIONS

Polypropylene mesh (Prolene), like that contained in the TVT-O, has many well-known characteristics that make it unsuitable for use as a product intended for permanent implantation in the human vaginal floor. These characteristics include the following: (1) degradation of the mesh; (2) chronic foreign body reaction; (3) infections and bio-films; (4) fraying, roping, curling and deformation of the mesh; (5) loss of pore size with tension; (6) fibrotic bridging leading to scar plate formation and mesh encapsulation; and (7) shrinkage/contraction of the encapsulated mesh.

As a result of these and other inadequacies with the mesh, and for the reasons set forth below, it is my opinion to a reasonable degree of medical certainty that the Prolene polypropylene mesh in the TVT-O causes a multitude of injuries, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, nerve injury of the obturator, pudendal and other pelvic nerves, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, Ethicon's TVT-O mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women.

A. The Prolene Mesh in TVT-O Degrades Over Time

As noted below, the mesh used in the TVT-O was originally designed in 1974 for use in

the abdomen for treatment of hernias and it has not changed since then.[1] Ethicon describes this mesh as the "old, old" mesh: "The first generation (old, old) mesh is utilized currently in the TVT product…."[2] The current Material Specifications for TVT-O Mesh list it as: "Old Construction PROLENE* Mesh."[3] Dan Smith testified that even when the original hernia mesh was updated for use in the abdomen, Ethicon continued to use the "old, old" mesh for TVT-O and does to this day, as follows:

> Q: So TVT kept the old when hernia changed to the new.
> A: Also known as original, yes.
> Q: The mesh that was used in the TVT-R is called sometimes by Ethicon in documents old construction or original mesh; correct?
> A: Yes. Yes.[4]

In the late 90's Ethicon determined that, in the hernia applications, it was safer to move to a lighter weight, larger pore mesh. Ethicon made a similar determination for meshes to be used in the pelvic floor.[5] However, Ethicon never updated the "old, old" hernia mesh used in the TVT-O.[6] Notably, in my opinion this makes science and information regarding hernia meshes and other pelvis meshes of particular relevance when discussing the TVT-O mesh as Ethicon chose to move to large pore, light weight meshes in these areas, but not for TVT-O.

The placement of permanent polypropylene mesh in the human vagina creates problems because of the chemical composition and structure of the mesh and the physiological conditions of the vagina and the surrounding tissues. There have been numerous studies over the last 30 years which have shown polypropylene to be chemically reactive and not inert, with flaking and

[1] Smith Dep. (2/3/2014) 723:9-724:6.
[2] ETH.MESH.09275875.
[3] ETH.MESH.10633520 at 3522.
[4] Smith Dep. (2/3/2014) 723:9-724:6.
[5] See, e.g., ETH.MESH.07455220 (discussing mesh shrinkage/contracture and stating: "Since this phenomenon occurs most frequently in small pore, heavy weight mesh, ETHICON has developed large pore, light weight meshes, i.e. GYNECARE GYNEMESH PS Nonabsorbable Prolene Soft Mesh….").
[6] Smith Dep. (2/3/14) 829:16-829:19.

fissuring demonstrated by scanning electron microscopy, which leads to degradation and release of toxic compounds into pelvic tissues. This process enhances the inflammatory and fibrotic reactions within the tissues in the pelvic floor, causing a multitude of problems.[7] There have been studies suggesting that oxidation of the mesh occurs because of the polypropylene and the conditions in which it is placed.[8] The oxidation causes the mesh to degrade, crack and break apart.[9] In a recent study, 100 pelvic mesh implants were compared and over 20% showed degradation to mesh fibers.[10]

Because of the structural complexities of the vagina and the nature of the chemicals ordinarily found in the vagina and its surrounding tissues**,** there are several reasons why polypropylene presents unique problems when placed in the vagina. An Engineering Bulletin from Propex, entitled "*EB-405, The Durability of Polypropylene Geotextiles for Waste Containment Application*," from 2011, states that, "[P]olypropylene is vulnerable to the following substances: highly oxidized substances such as (peroxide), certain chlorinated hydrocarbons (halogenated hydrocarbons), and certain aromatic hydrocarbons."[11] It is well known to physicians with expertise in the pelvic floor that vaginal and perivaginal tissues are ready sources for peroxide. The vaginal species lactobacillus produces hydrogen peroxide and lactic acid from collagen that is produced in the squamous cells of the vagina. Estrogen is the catalyst for the production of glycogen from the vaginal cells. It is also well known that hydrogen

[7] Coda A., *Hernia 2003*;7:29; Jongebloed, WL, "*Degradation of Polypropylene in the Human Eye: A SEM Study*," Doc. Ophthalmol., 1986 64(1:143-152); Skrypunch, O.W., "*Giant Papillary Conjunctivitis from an Exposed Prolene Suture*," Can. J Ophthalmology, 198621:(5: 189-192).

[8] Costello C., et al., "*Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Mesh Explants from a Single Patient*," Surgical Innovation , 2007, 143:168- 176).

[9] *Id.*

[10] Clavé A, Yahi H, Hammou JC, Montanari S, Gounon P, Clavé H, "*Polypropylene as a Reinforcement in Pelvic Surgery is Not Inert: Comparative Analysis of 100 Explants*," J Biomed Mater Res B Appl Biomater, 2007, Oct 83(1:44-9).

[11] *Citing* Schneider H., *Long Term Performance of Polypropylene Geosynthetics, "Durability and Aging of Geosynthetics, Koerner*, RM, Ed., (Elsevier 1989) 95-109.

peroxide produced by the lactobacillus species is important in controlling the vaginal micro-flora. In fact, the vagina is a ready source of hydrogen peroxide production. In a manuscript from M. Strus, "*The In Vitro Effects of Hydrogen Peroxide on Vaginal Microbial Communities*," the authors show the amount of hydrogen peroxide produced by the lactobacillus species.[12] "Hydrogen Peroxide reached concentrations of from 0.05 to 1.0 mm, which under intensive aeration increases even up to 1.8 mm."[13] These results confirmed the previous results of M. Strus in the publication, "*Hydrogen Peroxide Produced by Lactobacillus Species as a Regulatory Molecule for Vaginal Micro-flora*," Med Dosw Mikrobiol, 2004: 56(1:67-77).

It is also known that aromatic hydrocarbons can be found in the human body. In a paper from HB Moon entitled, "*Occurrence and Accumulation Patterns of Polycyclic Aromatic Hydrocarbons and Synthetic Musk Compounds in Adipose Tissues of Korean Females*," *Chemosphere* 2012 (86:485-490), these aromatic hydrocarbons were noted to be present in, "[t]otal concentrations of PAHs and SMCs in adipose tissues rang[ing] from 15 to 361 (mean:119) ngg(-1) lipid weight and from 38 to 253 (mean:106) nng(-1) lipid weight respectively . . . . The results of this study provide baseline information on exposure of PAHs and SMCs to the general population in Koreans."

It has also been determined that halogenated hydrocarbons can be found not only in adipose tissue but also the blood stream. A paper entitled, "*Determination of Volatile Purgeable Halogenated Hydrocarbon in Human Adipose Tissue and Blood Stream*," from the *Bulletin of Environmental Contamination and Toxicology*, Volume 23, Issue 1, pp 244 – 249 published

[12] Strus, M., et al., *The In Vitro Effect of Hydrgen Peroxide in Vaginal Microbial Communities*, FEMS Immunol Med Microbiol, 2006 Oct; 48(1:56-63).
[13] *Id.*

in 1979, found halogenated hydrocarbons, pesticide by-products, both in human adipose tissues and the blood stream. In a subsequent paper from 1985 in *Environmental Health Perspectives*, Volume 60, pp. 127-131, Henry Anderson, in his paper entitled, "*Utilization of Adipose Tissue Biopsy and Characterizing Human Halogenated Hydrocarbon Exposure*," also found these pesticide by-products in human adipose tissue. Accordingly, the body location where the polypropylene mesh is being placed can expose it to known chemical degradation agents.

However, chemical degradation is not the only way that polypropylene degrades *in vivo*. In a paper from N Das in the Journal of Biotechnology Research International, Volume 2011, Article ID 941810, entitled, "*Review Article: Microbial Degradation of Petroleum Hydrocarbons Contaminant: An Overview*," found that various bacteria such as Pseudomonas species, Bacillus species, Mycobacterium and Corynebacterium species, which are present in a woman's vagina, can degrade petroleum hydrocarbons. Also fungi such as the Candida species, also present, can degrade petroleum-based hydrocarbons.[14] Microbial agents that can be found inside the normal and abnormal flora of the human vagina such as Candida and, with certain pelvic infections such as Bacillus and Pseudomonas, can be a source of biological degradation of polypropylene products. A paper entitled, "*Health, Safety and Environment Fact Sheet: Hazardous Substances - Plastics*," from CAW/TCA (www.caw.ca), August 2011:343, found that polypropylene degradation products and residues can form carbon monoxide, acrolein, aldehydes and acids, qualifying these health hazards as toxic and irritants. In a paper from D Lithner in 2011 at 4, entitled, "*Environmental and Health Hazards of Chemicals in Plastic Polymers and Products*," University of Gothenburg, it is stated that, "[n]on-biodegradable polymers can be

[14] Das, N , et al., *Review Article: Microbial Degradadtion of Petroleum Hydrocarbon Contaminants: an Overview*, J Biotech Res Intl, 2011, Article ID 941810, 1-13.

degraded by heat, oxidation, light, ionic radiation, hydrolysis and mechanical shear, and by pollutants such as carbon monoxide, sulphur dioxide, nitrogen oxide and ozone. This causes the polymer to get brittle, to fragment into small pieces and to release degradation products." (Citations omitted.) Lithner continues, "[o]ther substances (besides monomers) are often needed for polymerization to occur, for instance initiators, catalysts, and, depending on manufacturing process, solvents may also be used. The resulting plastic polymer can be blended with different additives, for instance plasticizers, flame retardants, heat stabilizers, antioxidants, light stabilizers, lubricants, acid scavengers, antimicrobial agents, anti-static agents, pigments, blowing agents and fillers, and is finally processed into a plastic product. There are many different plastic polymers and several thousand different additives, which result in an extremely large variation in chemical composition of plastic products." *Id.* at 6 (citations omitted). "Since plastic products are composed of many different chemicals, and the main part of these [are] broken down into something completely different; this complicates the prediction." *Id.* at 8. "The type and quantity of degradation products formed may also be influenced by degradation mechanisms, presence of polymerization impurities, and surrounding factors, e.g. temperature and oxygen." *Id.* at 9. "Few studies combining leaching tests with toxicity tests have been performed on plastic products." *Id.* at 12. The available peer-reviewed literature regarding degradation/oxidation of polypropylene in the human body dates back to the 1960's and has been reported in numerous such publications.[15] Two of the more important and salient articles regarding reported degradation in explanted surgical meshes (hernia and pelvic floor) are the Costello and Clave articles.

[15] Liebert, T, et al., *Subcutaneous Implants of Polypropylene Filaments*, J Biomed Mater Res. 1976 (10:939-951); Williams, D., *Review of Biodegradation of Surgical Polymers*, J Materials Sci, 1982 (17:1233-1246); Oswald, H.J., et al., *The Deterioration of Polypropylene By Oxidative Degradation*, Polymer Eng Sci, 1965 (5:152-158).

In his paper, "*Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Implants from a Single Patient*," Prof. C Costello reported that hernia mesh made of polypropylene oxidized and degraded as a result of the metabolites produced by phagocytic cells during the body's inflammatory reaction to the mesh. High-magnification photographs showed cracking and peeling of the polypropylene fibers. Ethicon referenced this article in internal emails.[16]

Another article by A Clave, "*Polypropylene as a Reinforcement in Pelvic Surgery is Not Inert: Comparative Analysis of 100 Explants*," also displayed high magnification photos of polypropylene fibers from explanted meshes and, in this case, the meshes were explanted from women's pelvic floor tissue.[17] The heavyweight meshes showed even greater cracking than the lower density meshes, but according to Prof/Dr. Clave, ALL 84 of the polypropylene explants examined showed degradation. Oxidation of the implanted mesh due to free radical attack through the synthesis of peroxides, superoxides and hypochlorous acid during the chronic inflammatory phase was listed as just one potential cause for the oxidative degradation within the "septic environment" in which the pelvic meshes are placed.

Ethicon's Daniel Burkley, a Principal Scientist at Ethicon, testified that the science supported the conclusion that mesh could shrink, contract and degrade. Specifically, Mr. Burkley agreed that the risk of degradation increases when you have a severe inflammatory response with mesh implanted in a contaminated field.[18] Mr. Burkley also testified that polypropylene mesh in human beings is subject to some slight degree of surface

[16] ETH.MESH.005588123.
[17] Clave, A., *Polypropylene as a Reinforcement in Pelvic Surgery is Not Inert: Comparative Analysis of 100 Explants*, I Urogynecol J 2010 21:261-270.
[18] Burkley Dep. (5/22/13) 184:17-24.

degradation.[19] He agreed that degradation might be better understood if Ethicon studied or tested a product that is permanently implanted in women.[20] In fact, according to Mr. Burkley, Ethicon only conducted one study related to degradation and Prolene material. This study consisted of a Prolene suture implanted into dogs.[21] Mr. Burkley testified that the study and photos from the dog actually showed that the Prolene material used in TVT-O degraded and was still degrading after 7 years.[22]

Ethicon hired an outside consulting firm to resolve the cause of the erosion of its surgical meshes for the pelvic floor. In a June 22, 2011 report, PA Consulting Group informed Ethicon that, "[p]olypropylene can suffer from degradation following implant . . . a process which initiates after a few days post implantation in animal studies."[23] The consulting report discusses numerous images of polypropylene mesh that show "physical degradation" of the mesh.[24] In addition, in a 2009 presentation, Ethicon Medical Director Piet Hinoul stated that meshes are not biologically inert.[25]

I have personally seen mesh that is broken, cracked and looks different from when it came out of the package. Interestingly, despite years of scientific literature, its own internal dog study and reports from consultants it hired that degradation of mesh occurs, Ethicon's Instructions for Use (IFU) continues to claim to this day that the mesh in the TVT-O, "is not absorbed, nor is it subject to degradation or weakening by the action of enzymes."[26] This is not

[19] Burkley Dep. (5/22/13) 206:2-11.
[20] Burkley Dep. (5/22/13) 206:12-25.
[21] ETH.MESH.05453719 (Seven year data for ten year Prolene study: ERF 85-219).
[22] Burkley Dep. (5/23/13) 315:8-13.
[23] ETH.MESH.02589032 and ETH.MESH.07192929 (May 18, 2011 PA Consulting Report: Investigating Mesh Erosion in Pelvic Floor Repair and PowerPoint presentation).
[24] *Id.*
[25] ETH.MESH.01264260 (Presentation, "Prolift+M," P Hinoul, MD, Ethicon Pelvic Floor Expert's Meeting – Nederland, Utrecht, May 7, 2009).
[26] ETH.MESH.02340829 at 0835 (original TVT-O IFU), ETH.MESH.0234092 at 0908 (current TVT-O IFU).

simply inaccurate, but is false and misleading for all of the reasons stated above, including, most importantly, that Ethicon's own internal documents and testimony from its employees confirm that the mesh degrades.

It is my opinion to a reasonable degree of medical certainty that the mesh used in TVT-O degrades. The effect of chemical and biological degradation of the TVT-O Prolene mesh in a woman's tissues can lead to a greater foreign body reaction, enhanced inflammatory response and excessive scarring, which can lead to severe complications in patients, including the including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon's TVT-O mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women.

Given the information available in the scientific and medical literature concerning the potential for degradation of polypropylene, it is my opinion to a reasonable degree of medical certainty that Ethicon should have conducted clinically relevant testing to determine if naturally occurring conditions in the vagina could cause polypropylene to degrade and if so, what the quantity and quality of the products of degradation would be, whether they would be released into surrounding tissues and/or migrate in the woman's body, what the clinical implications for the woman would be and whether some women's body's would react differently to the mesh and the degradative process and its by-products.

Moreover, Ethicon failed to inform physicians or patients about the potential for

degradation of the mesh and the complications that could follow. In fact, Ethicon not only failed to disclose these risks to physicians and patients, it did not accurately describe these significant risks by calling them "transitory" and by putting inaccurate statements about degradation in its IFU. This is information physicians need to know in order to have a fair and proper conversation with their patients about the use of a product. Physicians rely on device manufacturers to inform them of the risks and complications associated with its products instead of downplaying them or inaccurately stating them. By not disclosing this safety information to physicians and their patients, it is my opinion to a reasonable degree of medical certainty that Ethicon failed to properly inform physicians and patients about the risks of degradation of Prolene mesh in the TVT-O. In addition, by failing to inform physicians, Ethicon did not provide them with an opportunity to discuss these risks with their patients.

B. Chronic Foreign Body Reaction

The human body has a natural and fairly predictable "host defense response" to any foreign object placed inside of it. Whether a splinter or a surgical mesh, the human body will send white blood cells to attack the invader and, if the products of inflammation cannot ward off or destroy the invader, including if the invader is anything from bacteria to prosthetic implants, the initial acute inflammatory phase is followed by a chronic inflammatory phase. Therefore, with the placement of something like a permanent surgical mesh in human tissues, there will be a chronic or permanent foreign body reaction to the implant, as well as a chronic inflammatory response by the body.[27] In fact, Ethicon Medical Directors, Piet Hinoul and Charlotte Owens,

[27] Klinge, U., et al., *Shrinking of Polypropylene Mesh In Vivo: An Experimental Study in Dogs*, Eur J Surg 1998, 164: 965-969; Klinge, U., *Foreign Body reaction to Meshes Used for the Repair of Abdominal Wall Hernias*,Eur J Surg 1998, 164:951–960; Klostherhalfen,B., *The lightweight and large porous mesh concept for hernia repair*, Expert Rev. Med. Devices 2005, 2(1); Binnebosel M, et al., *Biocompatibility of prosthetic meshes in abdominal surgery*, Semin Immunopathol 2011, 33:235-243; ETH.MESH.03658577 (Biocompatibility of Ultrapro).

have both testified that the chronic foreign body reaction created by the body's response to mesh can cause a severe inflammatory reaction, which can cause chronic pain, nerve entrapment, erosions, dyspareunia and the need for additional surgeries.[28]

This is of particular concern with regard to the TVT-O device because of its unique passage. For example, Professor de Leval, the inventor of the TVT-O, expressed his opinion that the development of pain (a significant issue with TVT-O as discussed below) is in part caused by a foreign body reaction to the mesh in close proximity to the obturator nerve bundle and its passage through the muscles of the leg. The report of a meeting with de Leval states as follows:

> He is convinced, however, that the foreign body reaction of the mesh in the trajectory outside of the obturator membrane plays a role in the development of pain…. [The mesh] sits close to the peripheral branches" [of the obturator bundle]….
>
> The second source of pain comes from the presence of the tape in the adductors…. This is of specific importance in young, active and/or sportive patients.[29]

Other consultants and experts in the field informed Ethicon that there would be chronic tissue reaction to its polypropylene meshes. During a 2006 meeting at one of Ethicon's facilities, Bernd Klosterhalfen, a pathology consultant expert for Ethicon, informed Ethicon that there can be a continuing reaction between tissues in the body and mesh for up to 20 years.[30] In addition, during a February 2007 meeting, Ethicon stated that there can be, "[E]xcessive FBR [foreign body reaction]> massive scar plate > more shrinkage."[31]

Internally, Ethicon's scientists agreed. Dr. Holste testified that chronic foreign body reactions occurs in Ethicon's small pore, heavyweight meshes like the Prolene mesh found in

[28] Hinoul Dep. (4/5/12) 99:09-25; (4/6/12) 518:14-520:20; (6/26/13) 175:1-176:17;184:18-22; 328:10-24; Owens Dep. (9/12/2012) 98:11-99:07.
[29] ETH.MESH.04050265.
[30] ETH.MESH.00870466 (June 6, 2006 Ethicon Expert Meeting Meshes for Pelvic Floor Repair, Norderstedt).
[31] ETH.MESH.01218361 (Ethicon Presentation: "State of Knowledge in 'mesh shrinkage'-What do we know").

TVT-O.[32] In fact, Dr. Holste testified that Ethicon developed lighter weight, large pore meshes in order to minimize the complications seen with heavyweight meshes like the Prolene used in TVT-O.[33] Ethicon employee, Christophe Vailhe, testified that there can be an excessive inflammatory reaction or foreign body reaction that would lead to mesh erosion and contraction.[34] Despite its knowledge about the problems associated with chronic foreign body reaction, Ethicon continues to use a heavyweight, small pore mesh in its TVT-O product.

Contrary to this scientific evidence, Ethicon informed doctors in its IFU that its TVT-O mesh was "non-reactive with a minimal and transient foreign body reaction."[35] This was despite all of the internal documents and testimony discussed above from Ethicon's Medical Affairs and Research and Development employees that chronic foreign body reaction occurs in small pore, heavyweight meshes like the Prolene mesh in TVT-O. Moreover, as one of Ethicon's lead engineers stated: "the foreign body reaction is not transitory – it doesn't ever go away, but decreases over time to a minimal level."[36] That is, it is chronic. I have reviewed numerous pathology reports from my own patients and other physician's patients and pathology reports reviewed in litigations describing foreign body reactions. Hence, the mesh potentiates a chronic, long-term inflammation. This is contrary to the express language of the TVT-O IFU and, to this date, has yet to be corrected in that IFU.

For the reasons set forth above, it is my opinion to a reasonable degree of medical certainty that the Prolene polypropylene mesh in the TVT-O creates a chronic foreign body reaction which can lead to severe complications in patients, including the possibility of multiple

[32] Holste Dep. (7/29/13) 52:5-55:21.
[33] Holste Dep. (7/29/13) 51:3-53:6.
[34] Vailhe Dep. (6/21/13) 383:8-19.
[35] ETH.MESH.02340829.
[36] ETH.MESH.00211259.

erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon's TVT mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women.

Moreover, Ethicon failed to inform physicians or patients about the potential for a severe, chronic foreign body response and the complications that could follow. In fact, not only did Ethicon fail to disclose these risks, it mischaracterized the risks by calling them "transitory" and by putting inaccurate statements about foreign body response in its IFU. This is information physicians need to know in order to have a fair and proper conversation with their patients about the use of a product. Physicians rely on device manufacturers to inform them of the risks and complications associated with its products instead of downplaying them or inaccurately stating them. By not disclosing this safety information to physicians and their patients, it is my opinion to a reasonable degree of medical certainty that Ethicon failed to properly inform physicians and patients about the risks of foreign body response of Prolene mesh in the TVT-O. In addition, by failing to inform physicians, Ethicon did not provide them with an opportunity to discuss these risks with their patients.

C. Infections/Bio-films

The placement of midurethral slings, including TVT-O, violates one of the most basic tenets of surgical teachings in that it is the placement of a permanent implant into the human through a "clean contaminated" surgical field, *i.e.* the vagina, which is not sterile and can never be completely sterilized, Therefore, implantation through the vagina is contraindicated for

every procedure and implantation.

In TVT-O, the weave of the mesh produces very small interstices which allow bacteria to enter and to hide from the host defenses designed to eliminate them. The bacteria can secrete an encasing polysaccharide slime (biofilm), which further serves to shield the bacteria from destruction by white blood cells and macrophages.[37] The effect and consequences of biofilm is to increase the foreign body reaction, resulting in chronic infections, chronic inflammation, erosions, and mesh and scar contracture, and was well known to Ethicon, as evidenced by the testimony of Ethicon's Head of Pre-Clinical, Dr. Joerg Holste.[38] Importantly, the biofilm actually serves as a protection for the bacteria surrounding the mesh fibers against the body's host defense response (white blood cells), which are intended to destroy foreign invaders like bacteria. Thus, the weave induces the creation of a shield against the body's defenses to the bacteria entrained in the woven mesh, inhibiting the body's ability to fight off the infective agents within the mesh. The large surface area promotes wicking of fluids and bacteria which provides a safe haven for bacteria which attach themselves to the mesh during the insertion process.[39] Daniel Burkley testified that reducing surface area could reduce the amount of chronic inflammation.[40] Additionally, the size of the mesh placed equates to a large surface area with many places for bacteria to hide while being protected from host defenses leading to

[37] Osterberg, B., et al., *Effect of Suture Materials on Bacterial Survival in Infected Wounds: An Experimental Study*, Acta. Chir. Scand 1979, 145:7 431-434; Merritt, K., *Factors Influencing Bacterial Adherence to Biomaterials*, J Biomat Appl 1991, 5:185-203; An, Y., *Concise Review of Mechanisms of Bacterial Adhesion to Biomaterial Surfaces*, J Biomed Mater Res (Appl Biomat) 1998, 43:338-348; The TVM Group: J. Berrocal, et al., *Conceptual advances in the surgical management of genital prolapsed*, J Gynecol Obsted Biol Reprod 2004, 33:577-587.
[38] Holste Dep. (7/30/13) 295:24-298:14, 411:15-414:24.
[39] Klinge, U., et al., *Do Multifilament Alloplastic Meshes Increase the Infection Rate? Analysis of the Polymeric Surface, the Bacteria Adherence, and the In Vivo Consequences in a Rat Model*, J Biomed Mater Res 2002, 63:765-771; Vollebregt, A, et al., *Bacterial Colonisation of Collagen-Coated Polypropylene Vaginal Mesh: Are Additional Intraoperative Sterility Procedures Useful?*, Int Urogyn J 2009, 20:1345-51.
[40] Burkley Dep. (5/22/13) 371.

numerous complications.[41]

There have been numerous peer-reviewed journal articles regarding secondary-mesh related infections as well as the dangers of implanting surgical mesh in a clean/contaminated field. Of note, in May of this year, at the AUA meeting in San Diego, Dr. Shah and his colleagues reported on the "*Bacteriological Analysis of Explanted Transvaginal Meshes*," which included explanted samples of both SUI slings and prolapse meshes. Of the 50 explants examined, 52% of those explanted due to patient complaints' of painful mesh were infused with pathogenic organisms, 20% of those explanted due to vaginal erosions had pathogenic organism, and 83% of those explanted due to urinary tract erosions were contaminated with pathogenic organisms.[42]

When polypropylene particles separate from the surface of the mesh fiber due to degradation, see infra, the surface area of the mesh is greatly increased thus providing even greater areas for bacterial adherence to the mesh, more elution of toxic compounds from the polypropylene, and also more of the free toxic polypropylene itself, all of which increases the inflammatory reaction and intensity of the fibrosis.[43] This cracking of the mesh surface also provides safe harbors for infectious bacteria to proliferate.

In his periodic histopathological analyses for Ethicon of its pelvic floor explants, Dr. Klosterhalfen reported to Ethicon that, in virtually 100% of those instances in which mesh had been explanted due to erosions, he found a secondary, mesh-related infection at the tissue/mesh interface.[44] Mesh exposure and erosion cause the fibers to be further exposed to bacteria that

[41] Klinge, *supra* n. 26; Vollebregt, *supra* n. 26.
[42] Shah, K., et al., Bateriological Analysis of Explanted Transvaginal Meshes (Abstract 1144).
[43] Jongebloed, *supra*, n. 1; Sternschuss, G, et al., *Post-Implantation Alterations of Polypropylene in the Human*, J Urol 2012, 188:27-32; Clave, *supra*, at 6.
[44] ETH.MESH. 00006636.

will adhere to and colonize on the mesh surface.

Ethicon employees have testified that they were aware of these biofilms forming on the surface of the mesh.[45] However, Ethicon never performed any long-term, clinical studies to determine whether the warnings given them through the peer-reviewed literature and by their own experts and consultants were accurate, namely that mesh-related infections are real; that they cause patient injury in the form mesh erosions and recurrent, late infections; and that the transvaginal implantation through and into the non-sterile, septic vagina is below the standard of care for any surgical technique, especially one used to treat non-life threatening conditions, such as stress urinary incontinence.

Therefore, it is my opinion to a reasonable degree of medical certainty that the TVT-O mesh is susceptible to biofilm formation due to the weave of the mesh allowing the infiltration, harboring, and protection of bacterial contaminants; the degraded mesh surface harboring bacteria; the passage through and into a clean/contaminated field; and after exposure/erosion of the mesh into the vagina or other organs, further contamination of the mesh with a multitude of vaginal flora that further increases the risk of harmful and recurrent infections in women. Accordingly, the TVT-O transvaginal technique, as well as the TVT-O mesh itself, are not safe for their intended purpose of implantation into a woman's pelvic tissues and can lead to severe complications in patients, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among

[45] Holste Dep. (7/30/13) 283:19-284:5.

others. As a result, the polypropylene in Ethicon's TVT-O mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women.

Finally, Ethicon's claims in its IFU that the TVT-O mesh may "potentiate infection" are misleading, at best. If, by the intentionally ambiguous term, "potentiate," Ethicon means "cause," then this is false for all of the reasons stated above. If by "potentiate," Ethicon means "exacerbate an existing infection," then the statement is misleading at best. Ethicon failed to warn physicians and patients that a slimy, protective biofilm could form on the mesh leading to painful erosions, recurrent, late infections and the need for mesh removal. The TVT-O IFU contrasts sharply with the PROLENE IFU on this issue. The PROLENE IFU states as follows: PROLENE Mesh in contaminated wounds should be used with the understanding that subsequent infection may require removal of the material.[46] Ethicon did not to include this risk, despite that unlike hernia mesh, TVT mesh is being implanted through a contaminated environment – the vagina. By failing to include this risk, Ethicon did not adequately warn physicians about these important risks, nor by extension, provide surgeons with an opportunity to discuss these risks with their patients.

D. Pore Size and Fibrotic Bridging

Fibrotic bridging occurs when the fibers surrounding the pores of the mesh are too close together to allow the tissue in the pore enough room to recover from the trauma of tissue damage due to implanting a surgical prosthetic device. Pores that are large enough for good, newly-vascularized tissue tend to be filled with fatty tissue versus small pores that become filled with scarred or fibrotic tissue. In those instances, the scar forms across the pores or "bridges" from

[46] ETH.MESH.02342102

one side of the pore to the other. This can occur either due to the granulomas around the mesh fibers joining together or due to densely-formed fibroblasts between these granulomas. Either way, such bridging can lead to the creation of a rigid, scar plate that can encapsulate the mesh with scar tissue. Simply put, small mesh pores that cause fibrotic bridging turn the mesh into a solid sheet of scar tissue and there is no space or room for tissue to grow into the mesh, which is the intended purpose of the mesh. The fibrotic bridging and scar plate prevents tissue in-growth and causes complications, including, among other things, pain with the rigid mesh, shrinkage or contraction of the mesh, erosions due to mechanical irritation in the tissue of a rigid, scar-plated mesh, nerve entrapment, chronic pain and dyspareunia.

This concept is best illustrated by a DVD produced by Ethicon which features an Ethicon consultant, Dr. Todd Heniford, talking about a heavyweight, small pore mesh called Marlex used for hernia repairs.[47] The Prolene mesh used in TVT-O is of heavyweight, small pore construction and, in fact, is even heavier than Marlex. Ethicon Scientists have acknowledged that the Marlex mesh in the video is similar to the Prolene in TVT-O in that is heavy weight small pore mesh.[48] In the video, Dr. Heniford talks about the dangers of heavy weight, small pore meshes.[49] In fact, Dr. Heniford states, "there is no excuse for using heavy weight, small pore meshes in the human body."[50] I have explanted numerous TVT and TVT-O meshes and have witnessed meshes with extensive scar plating and mesh encapsulation similar to the hardened/stiffened mesh viewed in the Heniford video.

I have reviewed the expert report of Dr. Uwe Klinge, in which he performed

[47] Heniford, B.T., 2007, *The benefits of lightweight meshes in Ventral Hernia Repair in Ventral Hernia Repair*, Video produced by Ethicon.
[48] ETH.MESH.05918776 (5/04/04 Email from Schiaparelli, Jill, Strategic Grown Subject: Marlex Experience); Batke Dep. (8/01/13) 87:12 - 88:10, 113:3-114:3, 257:23-259:13; Holste Dep (7/29/13) 51:3-53:6, 55:22-57:4; Vailhe Dep. (6/20/13) 182:2 185:5.
[49] Heniford Video, supra, n. 46.
[50] *Id.*

histopathological analysis on the same 23 explant samples of TVT and TVT-O that Dr. Jordi performed degradation testing. Dr. Klinge found that all of the pathology slides from these explants showed extensive fibrotic bridging and 19/21 showed folding or shrinkage. Dr. Klinge's description of these meshes is consistent with meshes I have personally seen in my practice.

In numerous emails, Ethicon employees discussed concerns regarding fibrotic bridging.[51] They have testified that the heavy weight, small pore type of mesh in the TVT-O can lead to an increased risk of foreign body reaction, contraction of the mesh, nerve entrapment, erosions and chronic pelvic pain.[52] In other emails, when discussing these concepts, Ethicon's World Wide Marketing Director for General Surgery, Marty Chomiak, states that "… we want to avoid 'bridging', therefore with think large pores are better than small . . ."[53] Ethicon also had information and scientific knowledge regarding superior mesh designs to prevent fibrotic bridging and scar plating. Specifically, Ethicon also had scientific knowledge that light weight, large pore mesh could decrease the likelihood of foreign body reaction, fibrotic bridging and scar plating.[54]

Despite having clinical knowledge of the importance of pore size to successful outcomes, and dozens of emails about the importance of pore size, Ethicon's person most knowledgeable

[51] ETH.MESH.04037600 (Innovations in mesh development); ETH.MESH.05920616 (7/20/07 ; Emails from Chomiak, M. to Batke, B., et al. re Defining light weight mesh); ETH.MESH.05585033 (Boris Batke Presentation – Project Edelweis – Ultrapro); ETH.MESH.05446127 (3/13/2006 Emails from Holste, J. to Engel, D., et al.re Mesh and Tissue Contraction in Animal – "Shrinking Meshes?); ETH.MESH.05475773 (2/09/2007 Boris Batke, Ethicon R&D, Presentation: *The (clinical) argument of lightweight mesh in abdominal surgery*); ETH.MESH.04015102 (3/1/12 Email from Batke, Boris to Mayes, C. re AGES Pelvic Floor Conference-Gala Dinner Invitation); ETH.MESH.04037600 (3/15/12 Boris, B. PowerPoint Presentation, *Innovations in Mesh Development*, Melbourne AGES 2012).

[52] Batke Dep. (8/1/13) 87:12-88:10, 113:3-114:3, 257:23-259:13; Holste Dep. (7/29/13) 51:3-53:6, 55:22-57:4; Vailhe Dep. (6/20/13) 182:2-185:5.

[53] ETH.MESH.05920616 (7/20/07 Email from Chomiak, M. re Defining Light Weight Mesh).

[54] Batke Dep. (8/1/13) 87:12-88:10, 113:3-114:3, 257:23-259:13; Holste (7/29/13) 51:3 - 53:6, 55:22 - 57:4; Vailhe Dep. (6/20/13) 182:2-185:5.

about pore size testified that Ethicon does not manufacture its mesh to a specific pore size. Dan Smith testified as follows:

> Q: Does Ethicon have a validated test method to determine the pore size of its TVT mesh?
> A: We determine the pore size by courses and wales and that is how it's done. So the courses and wale count is a validated test method.
> Q: And I'm talking about pore size. Does Ethicon have a validated test method to determine its pore size for its mesh?
> A: The construction of the mesh is -- does not have a pore size requirement.[55]

In fact, Ethicon does not even have a test to measure the pore size of its mesh. Dan Smith testified:

> Q. Mr. Smith, does Ethicon have a validated test to describe the pore size of its TVT meshes microns? Yes or no.
> A. No….[56]

Despite this information that it did not measure pore size or manufacture its mesh to a specific requirement, Ethicon repeatedly stated in advertising and marketing materials that its mesh was "large pore." For example, in one brochure, Ethicon promotes the mesh used in the TVT family of products (including TVT-O) as the "Largest pore size" of any of its competitors, listing the size as 1379 um.[57] However, given that Ethicon has no verified methodology to measure pore size, Ethicon had no scientific basis upon which to base these statements. In fact, in internal documents, Ethicon scientists described PROLENE mesh as small pore: "Standard Mesh PROLENE small pores area weight 105 g/m2."[58] One Ethicon Engineer measured a mesh and determined that there were two pore sizes in the mesh, a "major" and "minor" pore. "There are two distinct pore sizes in the PROLENE 6 mil mesh (TVT). The major pore is about 1176

[55] Smith Dep. (2-3-14) 729:1 to 729:12.
[56] Smith Dep. (2-3-14) 779:5 to 779:8.
[57] ETH.MESH.00349508 at 9510.
[58] ETH.MESH.04941016.

um…. The minor pore is about 295 um."[59] Certainly, neither of these pores was 1379 um, and the minor pore was substantially smaller.

In addition, the pore size of a mesh can change when the mesh is put under stress such as when a sheath is removed or the mesh is tensioned. Dan Smith agreed that these stresses can make an effective pore size smaller than 1 mm.

> Q. You would agree, Mr. Smith, that if the measurement across the pores we're looking at here -- let's assume you measure across one of those pores and let's say it's more -- let's say it's 1 millimeter across hypothetically. If a load is put on the mesh and it changes the pore size, that pore could be, after a load is put on it, under 1 millimeter; correct?
> A: It's possible depending on the load.[60]

Ethicon engineer Christophe Vaihle testified that "excessive tension on the mesh would lead to the decrease in pore size that can lead to poor tissue integration . . . ."[61] Ethicon has done nothing to change the mesh and continues to promote and sell the product with the same, heavy weight, thick filament "Old Construction 6 mil" mesh that they have been selling since 1974 (Prolene), despite what Ethicon considers to be "revolutionary" advancements in polypropylene mesh design that it brought to other pelvic floor polypropylene mesh products.[62]

In summary, for the reasons set forth above, it is my opinion to a reasonable degree of medical certainty that the Prolene polypropylene mesh in the TVT-O causes fibrotic bridging in the body, resulting in an increased inflammatory response leading to a multitude of injuries, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, dyspareunia that can be chronic, nerve injury, wound infection, rejection of the mesh, sexual dysfunction, urinary

[59] ETH.MESH.00584175 (Ex. T-3583); ETH.MESH.00584179 (Ex. T-3581).
[60] Smith Dep. (2/3/2014) 816:5 to 816:15.
[61] Vailhe Dep., (6/20/13) 224:10-226:21.
[62] ETH.MESH.03905968; *see also* Prolift +M CER ("As the mass of a mesh implant is reduced and the pore size is increased, the surface area exposed to the host is reduced, and the foreign body reaction to the implant is reduced.").

and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon's TVT-O mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women. Moreover, Ethicon did not inform physicians and patients that its mesh was susceptible to fibrotic bridging. Ethicon failed to warn physicians and patients that fibrotic bridging could occur leading to painful erosions, recurrent, late infections, nerve injury and the need for mesh removal. By failing to do so, Ethicon did not adequately warn physicians about these important risks, nor by extension, provide surgeons with an opportunity to discuss these risks with their patients.

E. Mesh Contracture/Shrinkage

By 1998, polypropylene mesh was known to contract or shrink 30-50%.[63] These findings were later confirmed in numerous papers, such as those by W Cobb and his colleagues – one of whom was Dr. Henniford (referenced above).[64] This also showed that heavier weight meshes like TVT-O led to greater amounts of contraction. The works of Cobb and Klinge/Klosterhalfen have been referenced in numerous Ethicon documents. Contraction or shrinkage has been shown to draw nerves close to the midurethral sling mesh both in the transobturator application[65] and for retropubic application.[66]

[63] Klinge, U, *Shrinking of Polypropelen Mesh in Vivo: An Experimental Study in Dogs*, Eur J Surg 1998, 164:965-969.
[64] Cobb, W., et al., *The Argument for Lightweight Polyropylene Mesh in Hernia Repair*, Surgical Innovation 2005, 12(1):T1-T7.
[65] Corona, R., et al., *Tension-free Vaginal Tapes and Pelvic Nerve Neuropathy*, J Min Invas Gynecol 2008, 15:3 262-267; Parnell, B.A., et al.,*Genitofemoral and Perineal Neuralgia after Transobturator Midurethral Sling*, Obstet Gynecol 2012, 119:428-431; Jacquetin, B, *Complications of Vaginal Mesh: Our Experience*, Intl Urogyn J, 2009, 20:893-6; Tunn, R, *Sonomorphological Evaluation of Polypropylene Mesh Implants After Vaginal Mesh Repair in Women with Cystocele or Rectocele*, Ultrasound Obstetrics Gynecol 2007, 29:449-452.
[66] Heise, C.P., et al., *Mesh Inguinodynia: A New Clinical Syndrome After Inguinal Herniorrhaphy?*, J Am Coll Surg

Furthermore, contraction or shrinkage is closely related to the pore size and weight of the mesh. Small pore, heavy weight mesh leads to fibrotic bridging which leads to scar plates, mesh encapsulation and shrinkage or contraction of the mesh, which is compounded by the shrinkage effect associated with the normal wound healing process already occurring in the tissue.

This phenomenon of shrinkage and its relation to the design of the pores as well as the consequences to the patient were illustrated in an email by Ethicon Scientist Joerge Holste in a March 13, 2006 email discussing a paper he authored entitled "Shrinking Meshes?"[67] In his email, Dr. Holste states "this was our scientific statement on mesh shrinkage: Basically, small pores, heavy weight meshes induce more fibrotic bridging tissue reaction causing more mesh shrinkage during maturation of the collagenous tissue. See my presentation about biocompatibility."[68] In addition, in a presentation by Boris Batke, Associate Director R&D, he states heavier-weight polypropylene mesh results in mesh contraction of 33%.[69] In an email dated November of 2002, related to a discussion of mesh used in a TVT product, Axel Arnaud, one of Ethicon's medical directors, used 30% shrinkage of the mesh as a "rule of thumb."[70] At an Ethicon expert meeting in Norderstedt, Germany in 2007, an Ethicon employee presented a PowerPoint entitled "Factors Related to Mesh Shrinkage" in which all of these issues were clearly laid out.[71]

In fact, in a March 6, 2012, response to a paper on mesh degradation, Ethicon wrote: "Since this phenomenon [mesh shrinkage] occurs most frequently in small pore, heavy weight

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1998, 187:5 514-8; Voeller, G.R., Surg Technol Intl 2003.
[67] ETH.MESH 05446127, *supra*, n. 34.
[68] Id.
[69] ETH.MESH 05479717 (3/1/11 Boris Batke, Ethicon Associate Director R&D, Presentation: Ethicon Polypropylene Mesh Technology).
[70] ETH.MESH 03917375.
[71] ETH.MESH. 02017152 (Nordestadt Expert's meeting 2007); ETH.MESH.01782867 (Factors Related to Mesh Shrinking).

mesh, ETHICON has developed large pore, light weight meshes, i.e. GYNECARE GYNEMESH PS Nonabsorbable Prolene Soft Mesh, GYNECARE GYNEMESH M Partially Absorbable Mesh."[72]

It is my opinion to a reasonable degree of medical certainty that as a result of work with internal and external experts and consultants in the late 1990s, multiple internal documents and articles, and the scientific literature as a whole, that Prolene mesh used in TVT-O not only could, but would shrink and contract, and that this shrinkage could lead to painful complications in women implanted with TVT-O, such as multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, nerve injury, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others.

As a result, the polypropylene in Ethicon's TVT-O mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women, and Ethicon failed to warn physicians and patients of the possibility of shrinkage and contraction and the adverse outcomes that could occur as a result.

F. Fraying, Particle Loss, Roping and Curling, Deformation and Loss of Pore Size

Ethicon designed the TVT-O mesh such that, when stress was put on the mesh, particles would separate from the mesh – this was called fraying or linting.[73] One of Ethicon's engineers described this as a "defect" that resulted from the method of cutting the mesh: "The mesh frayed

[72] ETH.MESH.07455220.
[73] Weisberg Dep. (5/31/13) 461:7-462:3 ("Q. So engineers within the company knew that fraying of the product was inherent in the design? A. Yes.").

is the reverse defect of the mesh features (elasticity of the mesh is one of the commercial arguments to market the TVT)…. [T]he root cause of this phenomenon are known: the way to cut the mesh (blade cutting). If we change the way to cut the mesh (ultrasonic cutting or laser cutting) it seems we can limit the mesh frayed defect significantly…."[74]

As early as 2000, Ethicon's engineers documented that particles from TVT Prolene mesh fell into women's tissues as a result of the tape edges being damaged during sheath removal.[75] In April 2001, Dr. Alex Wang, "one of the most experienced TVT users in the world," reported problems with frayed mesh and uneven tape width.[76] Although the issue was described as "serious" and as requiring "urgent attention and solution," Ethicon Medical Director, Dr. Martin Weisberg, simply concluded that the deformity in the mesh would be unlikely to have any clinical significance. Dr. Weisberg testified that although he did not actually know whether frayed mesh leading to particle loss would have clinical implications, he does not recall whether he or anyone else at Ethicon studied the issue.[77] Just a few months later, however, Ethicon received a complaint by an experienced surgeon regarding a patient who experienced vaginal wall erosion following a TVT procedure which was first noted by her husband during intercourse. According to the surgeon, "the tape appeared frayed and tiny fibers were protruding through the vaginal wall."[78]

In November 2003, Dr. Weisberg reported that there had been a total of 58 complaints of fraying with TVT since introduction of the device in 2000. He observed that the following

[74] ETH.MESH.01813975 at 2 (Ex. 3160/3587).
[75] ETH.MESH.01317515 (7/12/00 Preventia TVT-2 Risk Analysis Procedure/Tensioning Frayed Mesh/Particle Loss). at 7523.
[76] ETH.MESH.03905472 (6/4/01 Emails from Wang, A. re TVT Recommendation for Ethicon Study of Fraying/Particle Loss).
[77] Weisberg Dep. (5/31/13) 469:23-470:16.
[78] ETH.MESH.02621559 at 2276 (Ethicon Issue Report TVT Retropubic 2001 Open Date Between 01- Jan-2001 and 31-Dec-2001).

occurs when the mesh frays: "[T]he mesh elongates in places; the mesh narrows in places; and small particles of Prolene might break off … and that [s]tretching of the mesh increases the probability of fraying."[79] Once again, however, Dr. Weisberg concluded that "since fraying does not affect the safety and efficacy of the TVT device, it has been determined not to pursue any corrective actions at this time."[80] Dr. Weisberg confirmed during his deposition that no corrective action was taken and, although he did not know whether Prolene particles could elicit a chronic foreign body response, he does not recall whether he or anyone else at Ethicon investigated the issue.[81]

In 2004, Ethicon continued to receive complaints from surgeons about fraying and "brittle" mesh and particles falling into the operating field.[82] One of the company's "most urgent customers," Swiss surgeon Dr. J. Eberhard, wrote the following: "Already at the operation it is embarrassing to see how the tape is crumbling. But it gets worse if there is stretch on the tape.… I can't understand that no one will solve that problem for such a long time. As the latest, as the tape has becoming blue, everyone has realized that the quality of the tape is terrible."[83] Dan Smith, the Lead Engineer on TVT-O lamented the particle loss that was revealed when the mesh was dyed blue: "This is not going away anytime soon and competition will have a field day, major damage control offensive needs to start to educate reps and surgeons UPFRONT that they will see BLUE shit and it is OK."[84] Indeed in November 2004, one of the "top 3

[79] ETH.MESH.00541379 (11/18/03 Memo from Weisberg re Mesh Fraying for TVT Devices Inadequate Testing).
[80] *Id.*
[81] Weisberg Dep. (5/31/13) 469:23-470:16.
[82] ETH.MESH.00863391 at 3392 (2/27/04 Emails from Smith, D. re 2 TVT Complaints Concerning Allegedly Brittle Mesh).
[83] ETH.MESH.02180833 (11/12/04 Letter from Prof. Dr. Eberhard (translated)); ETH.MESH.02180828 (11/12/04 Telefax from Sibyll, B. re Prof. Dr. Eberhard).
[84] ETH.MESH.00863391.

complaints" included "Mesh frayed."[85] Once again, however, Ethicon decided to take no corrective action.[86] Instead, sales representatives were instructed to reassure their doctors that, "Prolene is proven to be inert," the "particles will not cause any problem," and to "be proactive" because "the competition will try to target this!"[87] Physicians were told the particles are "non-reactive" and that fraying does not affect the safety or efficacy of the device.[88] In fact, it has consistently been Ethicon's position that frayed mesh and resulting particle loss as well as roping, curling and deformation of the mesh do not create a safety risk and have no clinical significance.[89]

However, as noted above, Ethicon never tested whether the particles would have a negative clinical outcome. An independent investigator, Dr. Pariente, did and published a study that concluded that "the very high particle shedding for both Sparc (AMS) and TVT (Ethicon) may be of significant long term clinical concern in some quarters."[90] In addition, Ethicon collected data from physicians who informed Ethicon that particles could, indeed, cause pain and dyspareunia.[91] Although Ethicon claims that its own internal testing shows approximately 1% particle loss with TVT,[92] Dr. Pariente's study demonstrated TVT particle loss as high as 8.5% - 10 times higher than most of its competitors.[93]

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[85] ETH.MESH.01813975 (Ex. T-3160 / T-3587).
[86] ETH.MESH.02180826 (11/12/04 Email from Menneret, D. re Mesh Fraying: Dr. Eberhard Letter).
[87] ETH.MESH.00865322 (3/2/04 Email from Bell, S., Ethicon Marketing Director Europe to Sales & Marketing Team re Reminder on Blue Mesh – Frayed Mesh/Particle Loss).
[88] ETH.MESH.03535750 (10/12/2005 Hunsicker, K., Ethicon Clinical Operations Regional Manager, Presentation: *Investigator Initiated Study Process – Inadequate Testing*).
[89] ETH.MESH.00541379, *supra*, n. 58; ETH.MESH.00858252 (2004 Memo from London Brown, A. re Mechanical Cut v. Laser Cut Mesh Rationale).
[90] ETH.MESH.01221055 (Pariente, J-L, *An independent biomechanical evaluation of commercially available suburetheral slings*, Issues in Women's Health 2003).
[91] ETH.MESH.05644163 at 4166 (Dr. Hilton, one of Ethicon's principal investigators in the TVT v. Burch trial, informed Ethicon that: "The small particles migrate and cause pain during intercourse.").
[92] ETH.MESH.000585802; ETH.MESH.00585842; ETH.MESH.00585823 06/27/06 (Email from Kammerer, G. re GY: ***URHENT*** French STANDARD ON TVT & MESHES (COMMENTS REQUIRED)).
[93] ETH.MESH.01221055, *supra*, n. 67; ETH.MESH.00585842 (6/12/06 Email from Kammerer, G.re TVT LCM –

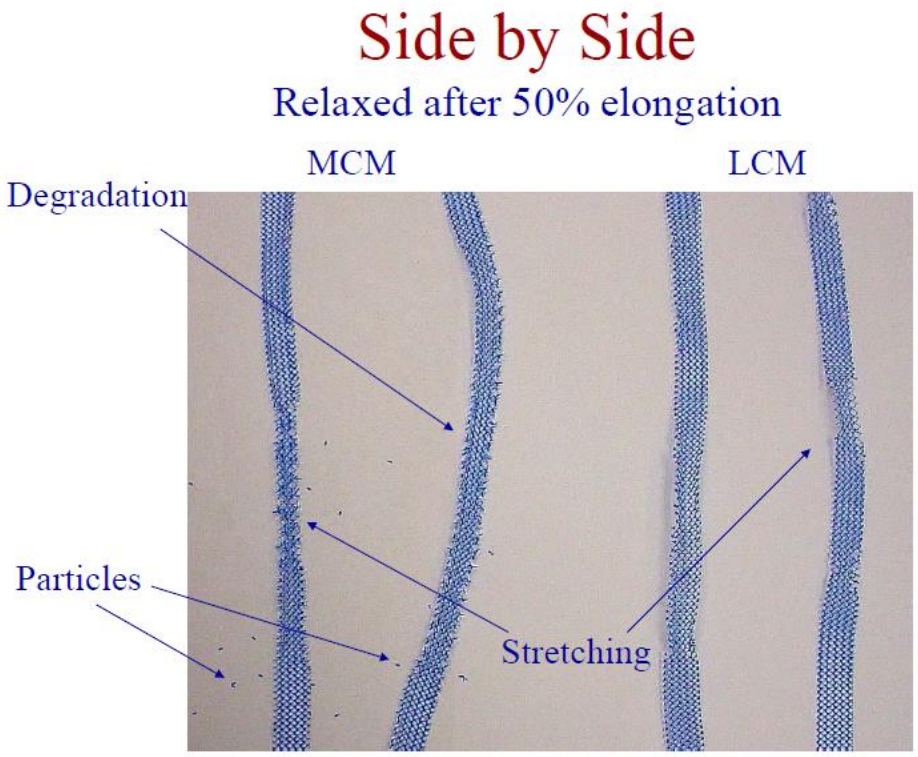
In addition, Ethicon's April 2006 Clinical Expert Report on Laser Cut Mesh suggested there was a decrease in particle loss with laser cut mesh and this "decrease would lead to less non-functioning material left in the tissues."[94] Interestingly, the greater the nonfunctioning material left in the patient's tissue, the greater the surface area of polypropylene the patient is exposed to, and the greater the inflammatory responses and the greater the foreign body response. As discussed above, the long term consequences of this chronic foreign body reaction and inflammatory response can be, among other things, chronic pain, lifelong risk of erosions, dyspareunia and failure of the device. If the individual flakes work their way through the vaginal mucosa, this can lead to dyspareunia and/or painful intercourse for the partner as noted in the complaint received by Ethicon back in 2001 referenced above. The larger the surface area the greater the risk associated with vaginal mesh. Finally, detached flakes of polypropylene may migrate into the vasculature or lymphatics and cause problems remote from the pelvis.

In addition to fraying and particle loss, the mechanically cut meshes used in TVT-O has also been shown to rope, curl and deform when under tension. In 2006, an Ethicon Engineer, Gene Kammerer, made a presentation that clearly showed each of these defects in the mechanically cut mesh. These photos clearly show particle loss, fraying, degradation, roping and deformation when the mechanical cut mesh was stretched and compared to TVT Laser Cut.[95]

Particle Loss (Reimbursement Submission)); ETH.MESH.01219629 (5/09/06 Email from Flatow, J.re Particle loss on TVT; ETH.MESH.01221024 (Kammerer, G. re New Standards for Urethral Slings); ETH.MESH.00585823.

[94] ETH.MESH.00167104 at 7109.

[95] ETH.MESH.08334245.



As noted these photos show mesh after 50% elongation. I have read depositions of Ethicon personnel claiming this is not a realistic elongation seen with mesh. However, Ethicon's engineer who took the photos, Gene Kammerer, explained that he had experienced it himself in testing:

> The link between the elongation percent, not force, and the integrity of the mesh is this. During the operative procedure as the surgeon removes the protective sheath from the mesh, the mesh stretches or elongates. It is my experience, after viewing many surgical procedures and performing numerous procedures on cadavers myself, that the mesh stretches approximately 50% at the maximum. There is also additional stretching that occurs if the surgeon elects to do an adjustment on the position of the mesh under the urethra. It is these two occurrences which produce the majority of the particle loss and loss of the integrity of the construction of the mesh.[96]

Again, Ethicon claimed that these problems with the mesh did not have any clinical

[96] ETH.MESH.00584811.

significance despite the fact that surgeons were complaining.[97] However, Ethicon's own internal documents demonstrate that this is not true. According to Ethicon's Failure Modes documents, the loss of pore size due to mesh narrowing or deformation can lead to urinary retention or erosion. Ethicon's own dFMEA from 2006 shows that the hazards of curling/roping, frayed edges and inadequate pore size of mesh can lead to the harms of erosion, recurrence, and pain.[98] When discussing the dFMEA for Laser Cut Mesh, Former Medical Director, David Robinson, agreed that pore size of both the Laser Cut and Mechanically Cut mesh "[c]ould reduce, the tissue might not encapsulate . . . the tissue might not grow through the mesh. It can become encapsulated and then it could cause . . . a rejection of the mesh."[99] And, Dr. Robinson testified that rejection of the mesh can lead to erosion.[100] These changes in the mesh may lead to erosion or pain for women with the deformed mesh implanted in their bodies. Further, according to Ethicon, this curling, roping or narrowing of the mesh may also cause urinary retention in addition to erosion and pain.[101]

In fact, I have witnessed the same type of roping and narrowing of TVT-O when I placed them myself and have seen and see the deformed and roped mesh when I remove them. This localized pressure under the urethra leads to complications like, among others, urinary retention, chronic pain, dyspareunia and erosions. In addition, I have reviewed Ethicon TVT training videos that show the exact problem discussed about related to deformation and roping of the "tape" under the urethra.[102] Finally, according to Ethicon's Dan Lamont, it chose to continue to sell "mechanically cut mesh despite knowing that it had the potential for degradation, particles

[97] ETH.MESH 00440005; ETH.MESH 00302390 (TVT-Base & TVT-O Review for Laser Cut Mesh (LCM) Risk Analysis).
[98] ETH.MESH.01218019.
[99] Robinson Dep. (9/11/13) 1070:23-1072:25.
[100] *Id.*
[101] Robinson Dep. (9/11/13) 1079:3-4-1081; 1081:9-13; 1083:8-18; ETH.MESH.01218019, ETH.MESH 01822361.
[102] ETH.MESH.PM.000004 (TVT Retropubic Implantation Video).

floating around in women's bodies, stretching, and roping . . ."[103] Lamont admitted that the fraying of the mesh was a "defect" of the mesh.[104]

Another feature of mechanically cut mesh is its sharp edges as shown on this photo: [105]

While Ethicon states that these sharp edges are part of the intended "velcro" effect of mesh, it was a feature about which Ethicon had received complaints tied to injuries and erosions. For example, during on market research test with physicians, it was reported:

> The surgeon felt that the MCM strips was elastic but with "hairs" on the edges and that it scratched with abrasive texture scraping (like the Scotch -BriteTM pads), furthermore a lot of particles were released and a rope/string effect could occurred if an excessive force was applied.[106]

In fact, when one agency recognized a spike in erosions, it inquired whether this was a result of "the cut ends of the tape appear to be sharper and more likely to cut tissue."[107] A sentiment shared by some physicians and reported to Ethicon:

Basically, he thinks that erosions due to the TVT mesh are underestimated in

[103] Lamont Dep. (9/11/13) 30:18-24.
[104] Lamont Dep. 9/11/13) 15:16-16:10.
[105] ETH.MESH.09656795.
[106] ETH.MESH.06696589.
[107] ETH.MESH.00330760.

> reports. The reason is that in order to recognize them, a very careful vaginal examination is needed. Most of the time, a "hidden" erosion is asymptomatic and neither the patients nor their sexual partner if any complain. But it might happen that a patient may complain. He believes that erosion are due to the sharp edges of the mesh. He wanted to suggest that we add to the mesh edges a kind of seam that would help preventing erosion.[108]

Dr. Axel Arnaud responded that Ethicon did not want to modify its mesh (even if it caused erosions) because Ethicon did not want to lose the marketing edge of using the Ulmsten/Nilsson data. He wrote:

> I also indicated that we want to be very careful with any modifications of our tape since a change in the mesh would obsolete all the long term clinical results we have about the procedure.[109]

However, the market pressure on Ethicon to create a laser cut mesh without particle loss, roping and deformation became very strong. Paula Evans, Gynecare European Marketing Manager, described the situation as "France is in a recovery mode, Germany is hemorrhaging business … Without laser cut, there is the real risk that more business will be lost."(sic)).[110] Hence, the laser cut mesh project went forward presumably in an effort to address the chronic problems with particle loss, fraying, sharp edges and elongation seen with mechanically cut mesh.[111]

During early development of laser cut, Ethicon acknowledged that mechanical cut mesh and laser cut mesh were two separate mesh products and to imply otherwise would be misleading. In December 2005, Kevin Mahar described the marketing strategy "…KEEP selling regular TVT (the 'Colonel's Original Recipe') to those customers that want/love it…and KEEP

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[108] ETH.MESH.03911107 (Axel Arnaud reporting his interview with Professor Hausler).
[109] *Id.*
[110] ETH.MESH.04985249.
[111] ETH.MESH.00301741 (11/21/05 Email from Lamont, D. re !!!!GREAT NEWS FOR TVT LASER CUT MESH!!!! –Frayed mesh/particle loss); ETH.MESH.00394544 (2/01/06 Global Regulatory Strategy – GYNECARE TVT – Laser Cutting Project); Weisberg Dep. (5/31/13) 487:13-488:7.

going forward with 8 years of data, etc with the original recipe … We do not mislead them that this is the same product…"[112] In discussing that document, Dr. Robinson verified that Mahar was referring to the mechanically cut mesh as the Colonel's Original Recipe:

> Q: He writes, "While we" -- "While we would work with our agency to get this right, my thoughts are that we keep selling regular TVT," meaning the mechanically-cut mesh, right?
> A. Yes.
> Q. "(The Colonel's 'Original Recipe') to those customers that want/love it." Right?
> A. Yes.
> Q. Talking about a piece of plastic that is permanently implanted in a woman's body as the "Original Recipe," right?
> A. That -- yes, that's correct.[113]

Ethicon initially decided that particle loss, elongation curve and flexural rigidity data on laser cut would not be required because they were not "critical to quality." In fact, this news was celebrated as "!!!!!GREAT NEWS FOR TVT LASER CUT MESH!!!!" and "less work for all of us."[114] However, because Ethicon wanted to continue to claim the marketing benefit of the Ulmsten/Nilsson series, marketing determined that some testing was needed. This was described as a way to protect the "clinical heritage" of the mesh:

> Marketing Need: Keep clinical heritage intact…. In order to continue to claim the use of 7-year data and all clinical studies, the MCM and LCM needed to show similar properties with the physical properties being used as a proxy for the clinical needs.[115]

However, the testing that was done revealed that laser cut mesh had substantially different physical properties than mechanically cut mesh particularly around elasticity and stiffness – laser cut was stiffer. In an internal memo documenting the results of TM403-477 (Ethicon's standard method for measuring tensile properties of TVT mesh), Ethicon reported that

[112] ETH.MESH.00687819 (Ex. T-3164).
[113] Robinson Dep. (7/25/13) 585:12-23.
[114] *Id.*; ETH.MESH.00584291 (2/15/06 Email from Flatow, J.re DVer protocol for particle loss).
[115] ETH.MESH.00858252; *see also* ETH.MESH.00526473; ETH.MESH.02248778 (Kammerer PPT); Hellhammer Dep. (9/11/13) 120-121.

the laser cut mesh was approximately three times stiffer than the machine cut mesh at one inch of elongation (or 20% elongation).[116] In March 2006, Gene Kammerer presented results from elasticity testing of mechanically cut and laser cut mesh showing laser cut mesh was less elastic (i.e., stiffer): "MCM [mechanically cut] meshes stretch between 55.8% and 33.4%. The LCM [laser cut] meshes stretch between, 39.5% and 32.1%."[117]

A stiffer mesh can change surgical techniques and outcomes. For example, in a February 2006 memo, Dr. Robinson explained that "a stiffer mesh will be more difficult to achieve proper tensioning without over tensioning…" Professor Carl G. Nilsson, who has been described by Ethicon as a "founding father" of TVT, stated he "will not use Laser-cut mesh!!" as it "does not have the same stretch profile of Mechanical-cut mesh."[118] The Laser Cut FMEA notes that if a mesh is too stiff it can cause the following harms: "Harm: Pain, Damage to Urethra, Urethral Impingement, Damage to Bladder."[119]

This difference in stiffness presented a problem for Ethicon because, as noted above, if laser cut was different than mechanical, marketing would not be able to use the Ulmsten/Nilsson data. Hence, in the March 2006 Clinical Expert Report for Laser Cut Mesh, signed by Drs. Weisberg and Robinson, Ethicon concluded that the two methods of cutting produce "meshes with statistically the same properties of elongation within approximately the first 4.0% to 5.0% elongation of the mesh."[120] Based upon this report, Ethicon decided a clinical study was unnecessary because the laser cut mesh was equivalent within this physiological range. [121]

However, as noted above, Gene Kammerer has estimated that during sheath removal the

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[116] Robinson Dep. (7/25/13) 507:18-508:1; Robinson Dep. (7/25/13) 509:6-21.
[117] ETH.MESH.00302181.
[118] ETH.MESH.04048515 at 8516 (7/01/08 KOL Interview: Carl G. Nilsson, Project Scion).
[119] ETH.MESH.01218019 (Ex. T-3175) (dFMEA for Laser Cut Mesh).
[120] *Id.* (Clinical Expert Report for Laser Cut Mesh)
[121] ETH.MESH.01784823 at 4828

mesh stretches up to 50%, not 4 to 5%. In this range, the bench testing showed that the two cutting methods produced two different meshes, with very different physical characteristics particularly relating to stiffness. The CER was inaccurate – laser cut was stiffer but Ethicon did not inform physicians because to do so would put marketing's ability to use the Ulmsten/Nilsson cases at risk.

Despite having testing showing that laser cut mesh behaves differently during implantation, Ethicon never performed a clinical study to determine whether the stiffness and other mechanical properties of laser cut mesh are better or worse than mechanically cut mesh.[122] Moreover, Ethicon did not track its complaints in a fashion to allow any such analysis to be done.[123] Finally, Ethicon did not warn physicians that the two meshes would act differently:

> Q. But they weren't telling doctors and physicians with the brochures, for example, that laser-cut acted any differently, right?
> A. I'd have to look at each of the brochures. But the one you showed me, no.[124]

In summary, for the reasons set forth above, it is my opinion to a reasonable degree of medical certainty that the Prolene polypropylene mesh in the TVT-O has several characteristics that make it improper for use in the vaginal canal including particle loss, fraying, roping, curling, deformation and loss of pore size. These unwanted characteristics can lead to, among other things, an increased inflammatory response (particle loss and fraying) and/or increased pressure on the urethra (roping or curling) or loss of pore size (roping or curling), and can lead to a multitude of injuries, including such as multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, recurrence, worsening incontinence, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction,

[122] Robinson Dep. (7/25/13) 521:25-522:4.
[123] ETH.MESH.00303084.
[124] Robinson Dep. (7/25/13) 577:18-578:10.

urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others. As a result, the polypropylene in Ethicon's TVT-O mesh (Prolene) is not suitable for its intended application as a permanent prosthetic implant for stress urinary incontinence in women.

Moreover, Ethicon did not inform physicians and patients that its mesh was susceptible to these physical deformations that could lead to painful erosions, recurrent, late infections and the need for mesh removal. Nor did Ethicon inform physicians that laser cut mesh had materially different mechanical properties than mechanically cut mesh. By failing to do so, Ethicon did not adequately warn physicians about these important risks, nor by extension, provide surgeons with an opportunity to discuss these risks with their patients.

G. Pain Syndromes

Perhaps the most common injury associated with the TVT-O can generally be described as "pain." This can present as groin pain, thigh pain, pelvic pain, nerve pain and in its more severe forms can be a debilitating injury transforming a woman's life. Immediately after the initial sales of the TVT-O, Ethicon received numerous reports of such pain. For example, one patient wrote:

> Four weeks ago I had the TVT put in. I have been in terrible pain ever since. It feels like something is cutting through my urethra every time I stand or sit down. This is a burning, intense pain. Doctor says it will go away in time. I was led to believe this was a pain-free, simple operation. It is terrible for me.[125]

Another TVT-O complaint was recorded as follows:

> The patient had a TVT-O placed about 3.5 weeks ago now and she is leaking and has 'severe'" -- in quotes, "'severe' right groin pain that is very tender to touch. The physician states he was contemplating removal, however, the physician that placed the device told the patient that if it is removed, she will have pain

[125] ETH.MESH.03574916.

'forever.'[126]

In response to these complaints, Ethicon's Medical Director, Dr. Charlotte Owens, performed a medical review of the complaints. After each review, her conclusion was generally the same: pain was a known, but "rare" complication with TVT-O and it was not "the fault of the device." For example, in response to the above complaint, Dr. Owens concluded:

Q April 11th, 2005 is your email saying, "I have reviewed the complaint. There is no evidence of device malfunction," right?
A Right.
Q So, in other words, it's not the fault of the device?
A Meaning the device performed as it was intended to.
Q "It is known that thigh pain rarely occurs after TVT-O."
A Correct.
Q And by "it is known," you mean Ethicon knows that after TVT-O procedure, thigh pain occurs?
A Ethicon and the surgeons know that after a TVT-O procedure, that thigh pain may occur rarely.
Q Rarely, and you write that, "rarely," right?
A Yes.[127]

However, as discussed below, it was evident from the original series of cases performed by Professor de Leval in 2003, that thigh/groin/leg pain was a common occurrence with TVT-O, not rare. In addition, Ethicon did not undertake any testing to determine the cause of the pain syndromes although it was clear that they were a result of the TVT-O procedure. Finally, Ethicon's description of the TVT-O induced pain in its IFU does not accurately capture the clinical picture.

Perhaps the clearest example of the clinical and scientific impact of pain syndromes caused by the TVT-O comes from the results of an independent study of the TVT-O that was performed by several of Ethicon's KOLs.[128] These investigators actually **stopped the trial**

[126] ETH.MESH.03575061.
[127] Owens Dep. (6/20/13)) 436:17 to 437:9.
[128] Teo, R., et al., *Randomized Trial of Tension-free Vaginal Tape and Tension-free Vaginal Tape-Obturator for*

because of excess pain reports in the TVT-O arm (26.4% pain reported at 6 months). The investigators concluded it was no longer ethical to use the TVT-O device given the clear negative impact on patient health. They concluded:

> **Concluding message**
> Although efficacy at 6 months is similar, TVT-O results in higher levels of postoperative pain and leg pain. These findings are similar to other studies comparing retropubic and transobturator tapes. Given the comparable efficacy of the procedures, it seems preferable to recommend retropubic tape placement to avoid a high incidence of leg pain.
>
> **Although the study was underpowered to detect differences in cure, the loss of equipoise from publication of results from similar trials necessitated the early termination of the study.**

This 2011 trial was not the first to show TVT-O caused leg/groin/thigh pain in more than one in four women who were implanted with the device. This was shown in Ethicon's original case series from eight years earlier.

The first TVT-O procedures were performed by Professor de Leval at the University of Liege. Ethicon funded these cases. In his earliest procedures it became clear that the procedure led to a large and noticeable increase over any other treatment of pain in the leg/groin area. In fact, in the Clinical Expert Report for TVT-O, Ethicon's Medical Director, Dr. Martin Weisberg, documented that in de Leval's first 138 patients "[t]he most frequent complaint in these 138 patients was postoperative thigh pain in 26 percent of cases."[129] Exactly the same percentages were found in *Teo* eight years later.

During the development of the TVT-O, Ethicon Senior Management questioned the cause of the pain and wondered whether a design change was necessary to avoid it:

> I wanted to be sure that you were made aware of this concern re transient leg pain [with the TVT-O]…. I do think we will need to hash out some solutions to this clinical issue:

Urodynamic Stress Incontinence in Women, J. Urol. 2011 Feb.; 185:1350-55.

[129] ETH.MESH.00259634 at 9638 (TVT-O CER December 2003).

1) Thoroughly understand the cause-effect of this complication – is it related to consistency of technique?
2) Can we avoid this clinical complication by changing technique alone (i.e. fine tuning the IFU)?
3) If the above two "reasons why" do not resolve this clinical outcome, then is there a design change that could avoid this complication? If yes, do we wait to make this change in the next gen product, or pursue the change now?[130]

The "reason why" TVT-O caused pain in over one in four of the women who received it was never determined by Ethicon prior to the launch of the TVT-O because Ethicon didn't have the time prior to launch to do a study. As noted throughout the design history documents of the TVT-O, Ethicon developed the TVT-O in a very aggressive timeframe. Dan Smith wrote the following shortly after launch:

> The [TVT-O] project was created in response to competition in France using trans obturator devices and rapidly stealing our TVT retropubic sales at an alarming rate…. The original product plan was estimated to be 24 months, which was honed to 18 months with a break through goal of 12 months. Upon chartering and increased market pressure eroding TVT base business the board issued a revised edict of <9 months or Y/E 2003. Unaware of how this goal would or even could be achieved, the team set out to do what was thought to be an impossible task regardless of resources or money…. Speed to Market: This project was completed in less than 9 months! A new record for Gynecare.

In fact, Senior Ethicon Management noted that completion of the TVT-O project in record time was "critical" to the success of the entire company:

> As you know, Project Mulberry [the development name for TVT-O] is critical to GYNECARE's success in the marketplace. The team has been charged with the breakthrough goal of completing this project in 9 months. We MUST make this project happen in a short period of time.[131]

In his document, "History of TVT-O" Axel Arnaud wrote:

> [T]he TVT sales started to slow down before really diving as it was obvious that the trans-obturator approach [of AMS's Monarc] was "better" than the retropublic

[130] ETH.MESH.03803462 (Email from Zenobia Walji).
[131] ETH.MESH.02180737.

> and the Company entered a critical phase of its existence since TVT was responsible for 65% of the sales. In front of this situation, I put all of my efforts in trying to find a better solution to avoid a disaster and I finally found in mid 2002 a Belgian Professor of Urology called J. de Leval….[132]

This rush to market dictated that Ethicon would not perform any testing to identify the cause of the pain. In fact, when a physician requested to participate in a safety study before launch, Ethicon told him they could not do such a study because they did not have sufficient TVT-O products made to do a study: "I may not be able to supply them the product needed for humans until much later in the year. I know that is not what you want to hear, but we are doing our best on this crash program."[133] Ultimately, the Ethicon Board made the decision "to take the risk of not requiring a clinical trial…."[134] As one of Ethicon's marketing personnel stated:

> At end of 2003 in the US, at this time we do not know how important it will be to launch in US immediately to if we will have time to wait until we have 3-6 months of US data. To protect our market share, we need to be ready to launch -- so the development process should not require clinicals.[135]

This time table led one Key Opinion leader to question whether Ethicon was doing everything it should to properly develop the TVT-O:

> I have a feeling that Gynecare is being pressured to get something out to market as soon as possible. Since the obturator approach has been described since 1999 why are you "now" looking at it? The R is coming after the D (R&D).[136]

In the end, Ethicon had clinical data only on 107 patients from deLeval's first study. Because of this, Ethicon sponsored a study with Waltregny and, by the time of launch, had data on 21 patients.[137] Hence, Ethicon launched TVT-O without studying why it caused

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[132] ETH.MESH.03932909 (Ex. T-3255).
[133] ETH.MESH.00864101.
[134] ETH.MESH.00858080; *see also* ETH.MESH.00858110 (April 10, 2003 meeting minutes from Project Leader Dan Smith: "[C]linicals will not be required for either Europe or USA" in order to meet "lofty break-through goal.").
[135] ETH.MESH.00260591 (April 14, 2003 email Cheryl Bogardus to Dan Smith and Brian Luscombe).
[136] ETH.MESH.00864132.
[137] ETH.MESH.00259634 at 9642 (Ex. T-336) (TVT-O Clinical Expert Report).

leg/groin/nerve pain issues in over one quarter of all patients, many severe and debilitating.

When preparing the IFU, Ethicon employees questioned whether to leave pain out of the document. It was determined, however, to add pain as a "Warning" using the following language: "Transient leg pain lasting 24-48 hours may occur and can usually be managed with mild analgesics."[138] This language, however, was inconsistent with the only results Ethicon had available to it – the de Leval data which showed it was not rare, was not transient, was not limited to the leg and was in some instances chronic and/or severe. This trend continued after launch of the product as well.

As noted above, after launch of the TVT-O, Ethicon immediately began to receive complaints regarding groin, thigh, leg, and nerve pain. Ethicon's response was consistently: it was not the fault of the TVT-O and it was rare.[139] As shown above, the primary source of this information was Dr. Charlotte Owens who was given the job of reviewing complaints and making these determinations and communicating them to physicians and patients. However, as shown in Dr. Owens's deposition, she was not given complete information about these issues. While Dr. Owens was informing physicians and patients that the pain syndromes they were experiencing from TVT-O were not the "fault" of the TVT-O, Ethicon senior management had already met "confidentially" with de Leval to discuss modifications to the design of the TVT-O to ameliorate the pain.

On March 22, 2004, three months after launch, Ethicon Senior personnel held a

[138] ETH.MESH.02340829 (TVT-O IFU)

[139] Owens Dep. (6/20/13) 444:6-445:2 ("Q: So we've just gone through, one, two -- five or so complaints that you received in a one- or two-month period in 2005, and they're all about leg pain associated -- leg or groin or thigh pain associated with the TVT-O, correct? A Correct. Q And in each instance, you determined that it was not related to the device, correct, except maybe that last one? A I think I said that I couldn't link it definitively or some other terms like that, so I'm not sure that there was a final conclusion. Q Now, you also used the phrase "rarely" a number of times. A Yes. Q Do you remember that? And you used "transient." A Yes. Q "Rarely occurs during TVT-O procedure," that's what you said, right? A Yes).

"confidential meeting" with Professor de Leval to discuss "possible modifications of TVT-O.[140] The group discussed various device modifications that would lessen the post-operative pain associated with the TVT-O. Despite this very early knowledge of potential design changes that could decrease pain syndromes for thousands of patients, Ethicon did not make any such change for years and instructed Dr. Owens to deny the device was causing the pain. However, during her deposition, Dr. Owens testified that when she gave such advice she did not know that the "confidential meeting" had occurred, nor did she know the belief of deLeval and others that modifications to the design might prevent the pain. She testified as follows:

Q Now, you remember throughout all of those leg pain emails, you also tended to reach a conclusion that the thigh pain was not the fault of the device, remember that?
A Right, meaning that the device did not malfunction.
….
Q Did anyone ever tell you that it was the design of the device itself that could have been causing the pain?
A I don't recall independently a conversation about that.
Q (By Mr. Zonies) Hand you what's called -- what I'm marking as 659, ETH.MESH number's 2180759. Now, this exhibit, I'm sure you've likely never seen before, right?
A Correct.
Q All right. And you see the date up there is March 29, 2004?
A Yes.
Q And it comes from the office of Professor de Leval at the University of Liege?
A Yes.
….
Q And he says, "You will find hereafter a summary of our confidential meeting held in Miami on the 22nd of March which relates to possible modifications of TVT-O."
A Correct.
….
Q All right. And then under Section 1, there's a bunch of French, and then it's translated into English where bold starts with one of the modifications, "Removal of the segment of the tape that passes through the adductor muscles (possibly causing postoperative pain)." Do you see that?

[140] ETH.MESH.02180759.

A Yes.
Q So, in other words, Dr. de Leval is saying, "Look, it could be the design of this tape, we should change the tape, maybe, and we can reduce the postoperative pain." That's what he's writing, right?
THE WITNESS: Not necessarily the design of the tape, but he's saying that it may be to the presence of the tape.
Q (By Mr. Zonies) Right, and that's the device causing that, right, that's the tape?
A Yes.
….
Q And there are a bunch of people who were very involved in the TVT-O from Ethicon at this meeting, Dan Smith, who was the project manager, Janice Burns, who was also very high up in the project, Axel Arnaud, right?
A Yes.
Q And they're all sitting in a conference room and having a confidential meeting about what to do about all the pain associated with the TVT-O, right?
THE WITNESS: Again, to do with the thigh pain that they're talking about, yes.
Q (By Mr. Zonies) And they're coming up with modifications to the device that may actually help resolve this pain issue, right?
A Correct.
Q (By Mr. Zonies) And yet every time, a year later, when you reviewed a complaint, you said it wasn't the fault of the device, but that's because you didn't know this, did you?
THE WITNESS: This is the first time I've seen this document….
Q You would have liked to have known that when you were trying to assess what was going on, wouldn't that have been helpful for you?
A Potentially.[141]

In addition, Dr. Owens testified that when she was informing physicians and patients that pain syndromes were "rare" she was not aware that Dr. Weisberg had concluded that in deLeval's early cases over one quarter of all patients had experienced pain:

Q The most frequent complaint in these 138 patients was postoperative thigh pain in 26 percent of cases.
A Correct.
Q So more than one out of every four women who had this procedure experienced thigh pain, correct?
A Yes….
Q And that was -- that was the most frequent complaint, doesn't say rare,

[141] Owens Dep. (6/20/13) 453:24 to 460:19.

does it?
A No.
Q And you would never ever say that one in four patients experiencing an adverse outcome is rare, would you?
A I don't think it sounds rare, no….

Also, for some of deLeval's early patients the pain was severe and was not transient. Dr. Weisberg testified that he was well aware that some of deLeval's early cases had severe pain.[142]

When Dr. Owens left Ethicon, Dr. David Robinson became the Medical Director handling complaints. Shortly after he began, he saw the number of complaints concerning pain syndromes and he immediately inquired whether the IFU should be updated:

> I am concerned that I am seeing an occasional bleeding/hematoma/neural pain related to TVT-O. I am relatively sure this is happening … when the operator pulls the handle of the device toward him/herself as the handle is rotated and moved back toward the midline. By doing so, the exit point of the trocar moves much closer to the obturator foramen…. I am concerned that we are now aware of this information and how should it be integrated into our training and IFU for TVT-O. Do we need to include a warning/precaution?[143]

No such modification to the IFU occurred.

Instead of fixing the TVT-O, Ethicon began development of the Mini-O or Abbrevo. This device was created largely to address the issue related to TVT-O and pain.[144]

In sum, de Leval's early cases reflected that over 25% of patients who have a TVT-O will experience leg/thigh/groin pain, that for some of those patients the pain will be severe and last more than a week. Prior to launch Ethicon never determined or studied the cause of this pain phenomenon. Ethicon launched TVT-O with an IFU that stated the following in the Warnings

[142] Weisberg Dep. (5/30/13) 197:17-198:7.
[143] ETH.MESH.00846523.
[144] Kirkemo Dep. (1/7/14) 389:20-394:15.

Section: "Transient leg pain lasting 24-48 hours may occur and can usually be managed with mild analgesics." Immediately after launch, Ethicon began receiving reports of severe, long lasting pain syndromes from TVT-O surgeries. Ethicon repeatedly informed physicians and patients that the pain syndromes seen with TVT-O were rare, transient and not the fault of the device. Within two months of launching TVT-O, Ethicon senior management met with deLeval to discuss modifications to the design of the TVT-O device to lessen its propensity to cause pain syndromes in patients. To this date, Ethicon has not modified the device nor revised the IFU regarding pain.

H. TVT-O IFU

The purpose of the IFU is for a medical device manufacturer to provide physicians with the information necessary for them to make decisions regarding the used a medical device for a particular patient. In addition, the IFU should disclose adverse reactions and risks known to the medical device manufacturer to the physician so that the risks can be relayed to the patient and an informed decision regarding the use of the product can be reached. Throughout my education, training, surgical and clinical practice, I have reviewed numerous IFUs for a variety of products, including mesh products in order to understand the proper way to use the device and to gain knowledge about the complications and adverse events associated with a device. I have extensive clinical experience with IFUs and instructing patients about the adverse events/risks contained in the IFU. Similar to Medical Directors, Dr. Martin Weisberg and Dr. David Robinson, I have gained expertise in IFUs through my extensive clinical experience reviewing IFUs, and consenting patients regarding IFUs, including Ethicon's own pelvic mesh products including the TVT line and Prolift.

Catherine Beath, Ethicon's former Vice President of Quality Assurance and Regulatory Affairs, testified that "physicians should be made aware of all the significant safety risks

associated with the product in the IFU."[145] And, "a reasonably prudent medical device company would continually update the label consistent with developing data and information that becomes known to the company" when it is appropriate.[146] Similarly, former Medical Director Dr. David Robinson testified that the warnings and adverse event section of the IFU should include all significant risks and complications related to the procedure and the mesh.[147] According to Dr. Robinson, a device manufacturer must include this information because you want to make sure the doctors have all the information they need to adequately inform patients who are deciding to use the product.[148] According to Ethicon Medical Director Dr. Martin Weisberg, the goal of the IFU is to communicate the most important safety risks attributable to the TVT device and that an IFU should never exclude known hazards or complications.[149] Dr. Weisberg also believes that an IFU should not knowingly underestimate the risks of using the product.[150] And, if an IFU excludes known complications or understates the risks, it "fails in one of its principal purposes."[151]

As noted above, the TVT-O project was completed in "record time." This affected the TVT-O IFU. When working on the IFU, project team members noted that "[w]e are on a very aggressive timeline with this project…." In response to an email regarding certain language changes regarding "safety," Sean O'Bryan, the regulatory lead on the project refused to allow the changes stating: "Although I appreciate and agree that all of these points of clarification are good, they need to be kept as "points of clarification" for translation purposes and not changes to

[145] Beath Dep. (7/12/13) 592:7-11.
[146] Beath Dep. (7/11/13) 198: 8-13.
[147] Robinson Dep. (9/11/13) 238:12-25.
[148] Robinson Dep. (9/11/13) 239:1-11.
[149] Weisberg Dep. (8/9/13) 659:19-660:15.
[150] *Id.* at 960:13-16.
[151] *Id*. at 961:10-17.

the IFU at this point. Clearly this IFU (and most I have seen) could be improved upon, however in the interest of time and resources, a line must be drawn…." The rushed timelines led to some serious errors in the IFU drafting in addition to the issues regarding pain described above.

1. Ethicon Chose Not to Include Important Safety Information in the IFU Because It Would Delay the Launch of the Product

On November 26, 2003, one month before TVT-O launch, Professor deLeval (through Waltregny) sent Ethicon his comments about the IFU. He was concerned that the IFU was "too light." One of his major concerns was the absence of instructions to the physicians about how to initiate the dissection. According to deLeval, this was an issue of patient safety. He wrote:

> The 'blade' issue: We really agree that in future IFU editions (as of April probably) it should be clearly mentioned that an initial sharp dissection of the para-urethral tissues must be carried out and then dissection is further performed with the use of fine dissection scissors ... '. As far as the term 'intial sharp dissection' term is concerned, we understand that you strongly not desire to state 'scalpel' or 'blade' or 'cold knide blade' etc ... for medico-legal reasons. At least, this is what we have understood. However, you should understand that the use of a blade for this - we are sure – very important initial step is major. Indeed, the situation is not similar to Ulmsten's procedure, since the tape has a different orientation and it is important to stay away from the vaginal wall, **to avoid vaginal wall damage, e.g. with scissors, and to avoid vaginal wall erosion**. These reasons, as well as others, **make us truly believe that for safety considerations, it is most likely safer to educate physicians to use a blade for this initial step rather than not mentioning this and risking vaginal wall problems (erosion, dyspareunia, ...)**In addition, not all urologists and OBGYNs are familiar with Ulmsten's technique (it is likely that some of them have only performed or seen outside-in transobturator and have no idea how to initiate the sub- and para-urethral dissection ...).
>
> In fact, isn't there more danger to damage the urethra when the sagittal 1-cm vaginal incision is carried out? Surprisingly, there is not much detail in the IFU and other documents on how to carry out this vaginal incision. Should it be 2 or 3 mm deep? etc ... Shouldn't it be added that care must be taken not to perforate the urethra?
>
> From this, you can understand that Professor does not want to be responsible for a 'wrong' approach of the procedure. How detailed should the information be? For

> medico-legal purposes, it would seem that the IFU, as is, may be too 'light'.[152]

When this e-mail was received by Ethicon, the Medical Lead for the TVT-O project, Dr. Weisberg, admitted that de Leval was right, the language should be in the IFU.

> Dr. Laval [sic] is correct. We should have stated that the incision should be initiated sharply and then dissected bluntly.[153]

But Weisberg stated that if Ethicon corrected the IFU, the launch of TVT-O would have to be delayed: "I spoke with Brian and he tells me that we cannot change the IFU without holding up the launch of the product." Ethicon then chose to launch the TVT-O without the critical safety language in the IFU. Instead, it would be added in the "next printing": "Can I presume for this next print of IFU this will be added? From your voice mail you say we have had 10,000 printed so I would guess from April onwards this will be in the implemented into the market place if our forecasting is accurate!"[154]

On March 1, 2004, as the next printing approached two months after launch of the TVT-O, Janice Burns the Marketing Lead of the TVT-O project, requested that the IFU be revised to include the "sharp dissection." She writes: "I would like to see the wording 'after initiating dissection sharply, continue using a push-spread technique,' Point 6."[155] A month later, on April 29, 2004, Janice Burns wrote another e-mail: "What has happened re the changes to the IFU?.... It appears to have gone quiet?"[156] Then, nine months later, on January 11, 2005, the issue finally resurfaced when Katrin Elbert sent an email to Ms. Burns and others with redlines of the potential change attached.[157] In fact, it was not until over 1 year after launch that the IFU was

[152] ETH.MESH>00865625 (Ex. T-487) (emphasis added).
[153] ETH.MESH.03715571 at 5573.
[154] *Id.*
[155] ETH.MESH.00866317.
[156] ETH.MESH.01814740 at 4741.
[157] ETH.MESH.00261818.

updated to include the proper dissection technique. Dr. Owens confirmed this in her deposition:

> Q: So until -- from the period of time of January, roughly January of 2004, through March of 2005, the language about initiating a sharp dissection was not in the IFU?
> A: Those words were not, no….[158]

As noted by Professor deLeval, the proper initiation of this dissection is a critical safety issue. If the dissection is not initiated properly, it can lead to a multitude of injuries, including erosion, perforation, nerve damage and pain syndromes. This is further corroborated by the dFMEA for the Mini-O or Abbrevo. There, one of the potential failure modes included use of the "Wrong scissors for dissection" and the harm associated with this issue was "nerve damage/pain (major)."[159] As Ethicon's Medical Director stated, the sharp dissection instruction should have been in the IFU. The failure to include this instruction could have led to significant patient injury.

2. The TVT-O IFU Failed to Inform Physicians About How to Properly Position Patients Leading to Leg, Groin, Hip and Nerve Injury and Pain.

During the development of TVT-O it was unclear to Ethicon employees how to properly position patients to maximize safety. At one point, Dr. Axel Arnaud wrote that the position should be "any position between the one used for TVT and the one described initially (hyperflexion)…."[160] During the drafting of the IFU, Ethicon employees discussed the importance of including a diagram of the leg positioning, particularly as it related to safety. For example, after a cadaver lab, one employee wrote about the feedback from the independent physicians regarding the leg position: "The concern raised by the doctors was that if we say to place the legs up "as much as possible" that there is a potential that the hips will be tilted not

[158] Owens Dep. (6/20/13) 390:1-5.
[159] ETH.MESH.00349122.
[160] ETH.MESH.00865147.

enough or too much – if tilted too much there is an increased potential for nerve impingement in this women. It was therefore suggested that a diagram would more clearly illustrate the degree to which flexion is required."[161] However, because of the lack of clarity regarding patient positioning, Dr. Martin Weisberg made a decision *not* to include a diagram in the IFU.

Immediately after launch of the TVT-O, Ethicon began receiving dozens of complaints about leg, hip and nerve pain, and it became clear that failure to properly position the patient was leading to injury. Dr. Aaron Kirkemo, later Ethicon's Medical Director, testified that for TVT-O proper leg positioning is critical to patient safety:

> Q. [T]he positioning can be critical to whether or not the patient suffers a nerve injury or if the patient has leg pain, hip injury, hip pain; correct?
> A. It's one of the mitigation strategies, yes.[162]

After the launch of TVT-O, independent investigators performed studies that demonstrated that if a patient is not positioned correctly, the needle trajectory will differ significantly potentially causing harm to obturator and pudendal nerves and blood vessels.[163] Yet, the TVT-O IFU was not modified to more accurately describe the proper patient positioning or to include a diagram.

Later, when creating the IFU for the Mini-O/Abbrevo, a procedure that uses the same leg positioning, Dr. Kirkemo and Dr. Hinoul (both of whom joined the company after the launch of TVT-O) insisted that a diagram of the leg position be included in the ABBREVO IFU as it was important to ensure patient safety. Dr. Kirkemo testified at length about an email exchange he had with his counterpart, Dr. Piet Hinoul, regarding the importance of having leg position in the IFU:

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[161] ETH.MESH.00260739.
[162] Kirkemo Dep. (1/7/2014) 434:9-15.
[163] Hinoul 2007; Hazewinkel 2009; Zahn 2007; Spinosa 207; Atassi 2008, Park Int Urogynecol J 2008; Paulson JSLS 2011, 15:326.

Q. "I think that it is critical that positioning be included in the IFU. If the patients aren't positioned properly I fear people will be placing the needle passes too far lateral to the ischiopubic ramus"; correct?
A. Yes.
Q. And what is the possible injury associated with that?
A. If you're too lateral, there's a chance of an obturator nerve branch injury.
Q. Nerve injury.
A. Yes.
Q. And that was your concern if you didn't put very clear -- and what ended up in Abbrevo -- pictures of how a patient should be positioned; correct?
A. Yes.
Q. And you ensured -- for the safety of patients and to avoid nerve injury and leg pain and to assure the proper passage of this device, the TVT Abbrevo, you ensured that the instructions for use clearly showed leg positioning; correct?
A. I did have that included in the IFU.
Q. And Piet's response was, "I am with you man!" That's what he says back to you. So the two physicians say, we need to ensure that other physicians understand this positioning by putting in pictures in the IFU. Right?
A. Yes.
Q. And if you take a look at the Abbrevo IFU that's in front of you … Exhibit 3469 is the Abbrevo IFU that you authored; correct?
A. I was involved with it, yes.
Q. And if you look at, in fact, the next page after the cover page, so the second page of Exhibit 3469, there, you have as the number 1 picture is how to position the patient on the table; correct?
A. Yes.
Q. That was important to you from a safety perspective that doctors understand that that's how patients should get positioned on a table; correct?
A. Yes.
Q. If you look at the 2010 to the present obturator IFU, same positioning. Right?
A. Yes.
Q. It's supposed to be.
A. Yes.
Q. If you look at the obturator IFU, Exhibit 3468, there is no such picture, is there?
A. No.
Q. Leaving patients at risk for mispositioning of their legs, nerve injury, leg pain, and hip pain; correct?
A: Potentially.
Q. And based upon that IFU and the comparison of the TVT-O without the picture showing physicians how to do it and the TVT Abbrevo where you insisted that the picture be in there about positioning, that Abbrevo instructions for use or IFU is safer; correct?
A: I think it incorporated what I thought were some, you know, updates that were important.
Q. It was a safer alternative.

A: A potentially safer alternative, yes.[164]

The TVT-O IFU to this day does not have the diagram, "leaving patients at risk for mispositioning of their legs, nerve injury, leg pain, and hip pain." During the development of the Abbrevo, the dFMEA clearly set forth the potential harms that could result from improper patient positioning, including:

> Patient hips not flexed enough – nerve damage / pain (major)
> Patient hips are not abducted sufficiently – nerve damage / pain (major)
> Patient is hyperflexed for too long – nerve damage / pain (major)[165]

This was especially true for elderly patients and those with arthritic issues.[166]

3. Tensioning and the Babcock.

TVT stands for and has consistently been marketed by Ethicon as "Tension-free Vaginal Tape." Presumably, this means the mesh should be inserted under the urethra without tension. However, the term "tension-free" is misleading. In practice, too little or no tension results in failure to treat the underlying condition of urinary incontinence. On the other hand, as suggested by Ethicon's own internal documents, too much tension can result in serious complications such as retention and urethral erosion.[167]

The IFU provides little guidance on proper tensioning of the TVT and TVT-O. Specifically, once the tape is placed, surgeons are simply instructed to "Position the tape loosely e.g. without tension, and flat under the mid urethra. At this stage a cough test can be performed. This allows adjustment of the tape so that only a few drops of urine are lost during the cough."[168] The IFU's Warnings and Precautions section cautions surgeons to "[e]nsure that the tape is

[164] Kirkemo Dep. (1/7/14) 437:4-440:16.
[165] ETH.MESH.00349122.
[166] Kirkemo Dep. (1/7/14) 363:3-365:1.
[167] ETH.MESH.05529274; ETH.MESH.04044797; ETH.MESH.05529653; ETH.MESH.00161131.
[168] ETH.MESH.02340829 (TVT-O IFU).

placed with minimal tension under the mid- urethra." Yet in the very same section, the surgeon is instructed "to place the tape tension-free in the mid-urethral position" to minimize the risk of de novo detrusor instability. Finally, the IFU's "Adverse Reactions" section provides that "over correcting, i.e. too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction." The IFU's conflicting instructions with regard to tensioning of the tape, i.e. "without tension," "with minimal tension," "tension-free" and "overcorrecting, i.e. too much tension" are clearly confusing and inadequate particularly given that improper tensioning could lead to complications and, therefore, the IFU needed to be "clear."

The path for the TVT-O is significantly different than that for the TVT. Thus, one of the differences from this path was related to removal of the plastic sheaths once the mesh was in place. That is, because the plastic sheath was more difficult to remove, the tension of the tape would increase. During the development of the TVT-O, Professor de Leval used the "Babcock technique" to ensure that the tension on the mesh was proper.[169] De Leval would use a Babcock clamp to hold the mesh while he pulled off the sheath.

Ethicon did not want to include this in the TVT-O IFU. "Professor deLeval uses a Babcock clamp to place the TVT mesh tension free. We are not going to use this method at this time, however we discussed doing tests to ensure that the mesh is not damaged…. The reasons for use are as follows: 1st the mesh is maintained flat and cannot curl, 2nd the mesh in the 2-3 mm loop is maintained tension free during the adjustment phase of mesh insertion and 3rd the clamp is used as the guide and support as the plastic is removed to prevent overtensioning."[170] As noted above, as TVT-O was on a "record" breaking development pace, this testing was never done.

[169] ETH.MESH.06880472 at 0474 (de Leval, J., *Novel Surgical Technique for the Treatment of Female Stress Urinary Incontinence: Transobturator Vaginal Tape Inside-Out*, Eur. Urol. 2003, 44:724-730).
[170] ETH.MESH.00862727 (6/2/03 email from Dan Smith).

When Ethicon received de Leval's paper on how he performed his technique, Ethicon specifically requested that de Leval add a section into the paper *not* using the Babcock. "Regarding the section where he describes clamping the tape, we cannot ask him to remove this because this is what he did to perform the procedure. But, Axel, perhaps we can suggest that he include an alternative option to achieve the same desired result…."[171] Ethicon convinced de Leval to add this to his paper when it was published (even though it was not the technique he used).

Not only did Ethicon fail to perform the testing to determine whether the Babcock was necessary to successful outcomes with TVT-O, Ethicon also did not include the Babcock technique (even as an alternative) in its IFU to inform physicians about: (1) the different sheath pull off forces required for the TVT-O; (2) the impact on tape tension associated with the increased forces, including increased roping, fraying and a decrease in pore size; (3) the potential adverse events associated with tape tensioning, such as erosion, fibrotic bridging, retention, extrusion, pain, and nerve damage; and (4) methods to minimize the impact of tape tensioning such as the Babcock technique.

Upon launch, Ethicon immediately began to field complaints about the difficulty of sheath removal with the TVT-O. "Sheath Removal problem: Dr. Jensen indicates that the issues began almost immediately when he converted to TVT-O (estimated late Janaury/early February)."[172] According to Ethicon sales personnel, these were not isolated problems. As a sales representative in Dallas reported to the TVT-O development team, many physicians were experiencing these issues: "[T]he [sheath removal] issues experienced by Dr. Feagins are not unique to the Dallas market….they are being experienced by physicians all over the country and are creating serious

[171] ETH.MESH.03918552.
[172] ETH.MESH.06884516.

challenges for the sales representatives."[173] The Marketing Director and Co-Lead of the TVT-O Project noted her concerns that it was a worldwide ("WW") problem.[174]

To address this problem, Ethicon promoted the use of the "Babcock" technique – the very technique it refused to put in its IFU for TVT-O. But, Ethicon did not amend the IFU or add the language, instead, it chose to have its sales representatives inform physicians through a "tips and tricks" program.

> It is imperative that we communicate to the Field Sales organization how to handle these "sheath" issues by letting them in on the specific application "Pearls of Wisdom" that Dan Smith was able to pass along to Dr. Feagins. If we don't do this, we risk losing more ground to our competitors. Please confirm when and how we plan to pass on this critical information to the Field Sales organization.

In addition, Ethicon employees sent individual e-mails to physicians who called or e-mailed with complaints or concerns about the sheath/tensioning issues.[175] Ethicon was now promoting the very technique that it had earlier determined needed testing before putting it in the IFU. Ethicon used the "tips and tricks" to "buy time" while it determined why the TVT-O was essentially malfunctioning: "Implementing the DeLeval babcock tip/trick eliminates the problem of stretched mesh under the urethra and can buy time for us to understand what factors (patient size or tissue, product/manufacturing, surgeons, techniques) are driving variability in sheath removal in general TVT classic and TVTO."[176] Clearly, this was something Ethicon should have done before launch but did not.

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[173] ETH.MESH.01815505 at 5506.

[174] ETH.MESH.01815505 at 5512 ("From my perspective I strongly believe we have variability issues…. Having been in the OR with many surgeons the ease or difficulty of sheath removal can vary immensely…. Having spent time more time in the US this week this is a WW issue and not market specific.").

[175] ETH.MESH.00864413 (email from David Robinson MD to Dan Smith regarding deLeval's Babcock technique: "I have been employing the modifications listed below and they have been very helpful in easing sheath removal and preventing tape stretching.").

[176] ETH.MESH.01815505 (Ex. T-233).

In August of 2004, as complaints continued to roll in, Ethicon sales and marketing requested that the "Babcock" be put into the "Procedural Steps" document so all physicians would be informed: "Janice, how long has Professor de Leval been using the "babcock" – was this something he created? I am wondering if this should not be included in the "procedural steps?"[177] Janice Burns responded that any change to the Procedural Steps would also require a change to the IFU – something Ethicon was "hesitant" to undertake as it *still* had not performed the appropriate testing: "I hear what you are saying about introducing it in the procedural steps, however, what we include in the procedural steps has to reflect the IFU. Our hesitancy about doing this for launch was because we were not sure of any potential damage to the mesh caused by the babcock."[178] So Ethicon did not put in into the Procedural Steps either.

As one sale representative noted in an email to Dan Smith, the inability of Ethicon to properly communicate how to tension the TVT-O had safety and legal ramifications:

> I feel I got grilled on my suggestion of tensioning, yet there is no clear direction on tensioning…. My goal is not to get the tape changed, yet strive to place the mesh as designed without altering it. The surgeon does own the responsibility of proper delivery and placement. The fact is, they look to us as reps to show them the proper placement techniques.
> The reason for my question is to see if someone had the proper wording we need to use as reps that eliminates our liability with this product in the OR concerning tensioning.[179]

In my opinion, Ethicon failed to properly test the unique sheath removal and tensioning issues related to the TVT-O prior to marketing the device. Ethicon left physicians without sufficient information about how to properly remove sheaths and/or properly tension the TVT-O mesh. Ethicon improperly managed the sheath/tension problem by telling individual physicians "tips and tricks" including the Babcock technique. This advice necessarily could not reach

[177] ETH.MESH06881576 (August 16, 2004 email Kevin Mahar to Janice Burns re "TVTO").
[178] ETH.MESH06881576.
[179] ETH.MESH.00864503.

hundreds of surgeons who did not get the "tips and tricks" from sales representatives or Ethicon employees. Such information should have been put in the IFU. Because physicians did not have the proper information, they could not impart the information to their patients or properly consent their patients for all of the risks associated with overtensioning mesh such as roping, curling, fraying and all of the associated injuries.

4. The TVT-O IFU Did Not Include All Known Risks, Was Inaccurate and Was Not Updated.

a. The IFU did not include all known risks.

As noted above, Ethicon did not include the proper information concerning the dissection in the original IFU. There were also numerous other potential risks that were not included in the IFU at launch.

If you compare the adverse reactions/risks in the TVT-O IFUs to the adverse reactions/risks that were available and known to Ethicon at the time of the launch of TVT-O, it is clear that there are numerous adverse events absent from the IFU. For example in the TVT-O IFU at launch, the Adverse Reactions/Risks section read as follows:

ADVERSE REACTIONS

* Punctures or lacerations of vessels, nerves, bladder or bowel may occur during needle passage and may require surgical repair.
* Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation.
* As with all foreign bodies, PROLENE Mesh may potentiate an existing infection. The plastic sheath initially covering the PROLENE Mesh is designed to minimize the risk of contamination.
* Over correction, i.e., too much tension applied to the tape may cause temporary or permanent lower urinary tract obstruction.[180]

Despite only listing the above adverse reactions/risks, it is clear from the testimony of

[180] ETH.MESH.02340829.

Senior Ethicon Employees in both the Medical Affairs and Regulatory Affairs that every adverse reaction/risk that Ethicon has scientific knowledge of today, it had scientific knowledge about at the time the TVT was first sold in and certainly in 2004 when the first TVT-O was sold, marketed and launched. Medical Director, Piet Hinoul testified that Ethicon understood the following adverse events occurred from the time the TVT was first sold, years before the first TVT-O was sold:

Erosions through vaginal epithelium Infection
Pain
Urinary Problems
Erosions that could decrease patient's quality of life Dyspareunia
Need for additional surgeries
Need for the removal of device
Urinary Tract Infections
Dysuria
DeNovo Urgency
Mesh Exposure
Fistula Formation
Hematoma
Abscess Formation
Narrowing of vaginal wall
Erosion which can occur any time in future
Contracture of mesh causing pain
Complications making it impossible to have sexual relations
Worsening Incontinence

Yet, none of these were in the TVT-O IFU at launch.

In addition, as discussed more fully throughout this report, Ethicon failed to include significant risks in its IFU related to the Prolene polypropylene mesh, including potential cytotoxicity, association with tumor formations and that the mesh can degrade, shrink and contract. The IFU also fails to include risks associated with the Prolene mesh, including chronic foreign body reaction, fibrotic bridging, infections/biofilms, fraying/particle loss and roping/curling of the mesh.

Medical Director Dr. Weisberg testified that Ethicon did not include: "permanent,

lifelong, worsening and debilitating pain", lifelong risk of surgical repairs for erosions, "severe or chronic inflammation", collapse under strain and cause fibrotic bridging, that the product can degrade, that polypropylene is cytotoxic, severe erosion, or particle loss.[181] In addition, former Medical Director, Dr. David Robinson, testified that Ethicon never informed physicians that patients may require multiple surgeries to treat erosions, that erosions could be severe and untreatable, and that patients could endure lifelong severe pain or dyspareunia/painful sex. This is true despite, as discussed above, Ethicon had scientific knowledge of the risks at the time of launch.

b. The IFU inaccurately portrayed risks.

In addition to excluding certain known risks, Ethicon significantly downplayed the risks that it actually listed in its IFU. This is especially true with respect to erosions. On the topic of erosions, in the Adverse Event/Risks section in the TVT-O IFU, in place from the time of launch until present day, it states:

- Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation and inflammation.

This language significantly downplays the permanent nature of erosions and suggests to physicians that erosions are a "transitory" or temporary problem. As shown in an email exchange between Ethicon's Associate Medical Director of Worldwide Customer Quality Meng Cheng, M.D., Ph.D and Bryan Lisa in the Regulatory Affairs Department, it was clear that the adverse events were not "transitory." Chen wrote, "Pardon me again, from what I see each day, these patient experiences are not "transitory" at all."[182]

Ethicon also had scientific evidence that erosions could occur many years after

[181] Weisberg Dep. (8/9/13) 968:12-972:21.
[182] ETH.MESH.04093125 (1/29/09 Email between Meng Chen and Bryan Lisa).

implantation of the device. In Minutes from June 22, 2001 Scientific Advisory Committee on Pelvic Floor Repair, it was a "Consensus: Erosion is a risk. Erosion, possibly an infection response. Typically seen by 3 mos, usually by 6-12 mos. Can present late, 3 years. To vagina-not a good situation. To bladder, urethra or rectum-a very bad situation."[183] "There have been reports of erosions into the urethra that are not picked up until months even years after the procedure."[184] In October 2002, Medical Director Dr. Martin Weisberg was involved in email exchange with European Science Director Axel Arnaud about downplaying risks with respect to erosions. Specifically, Dr. Arnaud suggested to Dr. Weisberg that Ethicon needed "to be more elusive" when discussing potential complications like erosions.[185]

According to Medical Director Dr. Martin Weisberg and former Medical Director Dr. David Robinson, Ethicon never disclosed or warned doctors or patients in IFUs or Patient Brochures that the use of TVT-O slings can cause lifelong risk of erosions.[186] Despite the fact Ethicon had scientific feedback from one of its own doctors that experiences were not transitory and that she had concerns about the IFU and the transitory language, Ethicon never informed physicians or disclosed it in its IFU.

c. Ethicon failed to update the IFU.

Once TVT-O was on the market, Ethicon refused to appropriately update the IFU to reflect the known risks above and additional risks. As discussed above, when Dr. Robinson first began working at Ethicon, he asked about adding instructions to the IFU to avoid obturator nerve injury:

I am concerned that I am seeing an occasional bleeding/hematoma/neural pain

[183] ETH.MESH.02089392.
[184] ETH.MESH.04099233 (September 24, 2008 email from Melissa Day to Meng Chen and others).
[185] ETH.MESH.03910175-03910177.
[186] Weisberg dep. (8/9/13) 968:2-969:10; Robinson Dep. (9/11/13) 329:12-330:7.

> related to TVT-O. I am relatively sure this is happening … when the operator pulls the handle of the device toward him/herself as the handle is rotated and moved back toward the midline. By doing so, the exit point of the trocar moves much closer to the obturator foramen…. I am concerned that we are now aware of this information and how should it be integrated into our training and IFU for TVT-O. Do we need to include a warning/precaution?[187]

In another e-mail exchange, Dr. Robinson was told of a physician's technique that significantly decreased the incidence of pain from TVT-O. By this time he had concluded that company policy would make updating the IFU out of the question: "[I]t would require a cadaver study, maybe a pilot to confirm lack of problems, and then a revision of the IFU which can take 6 months or more to get done."[188] In another e-mail, Susan Lin recommended that the IFU not be updated because it would require updating other IFUs and might delay the launch of another product.[189]

On December 19, 2008, after Dr. Meng Chen had received a complaint from a number of patients about not being fully informed of the risks of the procedure, she recommended to senior management that the IFU be updated:

> [The patient] was given the most accurate consent for the potential adverse reaction known in 2005. However, we are in 2008 now, and there are two more TVT family products (TVTO and TVTS) on the market. Our post-market knowledge with these products are much more than what we have in the IFUs of all three types of TVTs (TVT-Abdominal, Obturator and Secur). My reason for bringing this point to you is maybe you may look into it from senior management perspective and to facilitate the IFU update for all three TVTs, particularly in the area of 'Potential Adverse Reactions'…. One of the paths for a better pre-operative consent is to provide an updated IFU to the operating physicians that reflecting the current knowledge of the manufacturer's on the potential adverse reactions."[190]

In a January 29, 2009 email, Meng Chen wrote again that the IFU should be updated to make it clear that the irritation and foreign body response were a result of the tape itself and that

[187] ETH.MESH.00846523.
[188] ETH.MESH.00832937.
[189] ETH.MESH.00211263 ("if we change it in TVT EXACT, we need to update TVT Classic IFU as well…which may impact our timeline [to launch]").
[190] ETH.MESH.04092868.

this "could result in tape extrusion, tape erosion, fistula formation or inflammation."[191] When working on the Mini-O/Abbrevo IFU, Ethicon employees noted that the older IFU's should be updated. Dr. Aaron Kirkemo wrote:

> I would agree from the meeting today that now that we have 12+ years of experience with TVT classic that learnings from the field would probably drive a relook at the TVT Classic IFU as reflected by some of your comments in this document."[192]

In response, Dr. Robison asked: "has there been agreement re: a project to revise TVT and TVTO?"[193] There was indeed agreement at upper management – there would be no revision to incorporate what they had learned: "Per Scott C and Stale, they just want to "look forward" with this project. Their plans are to leave TVT Classic [and TVT-O] as is. Aaron."[194]

Interestingly, in 2008, 2011 and 2012, Ethicon added numerous adverse reactions and risks to its Patient Brochures that have never been disclosed in previous versions of the Patient Brochures. These adverse reactions and risk have never been disclosed in the TVT-O IFUs even at present time. These risks are as follows:

> **From Patient Brochures (never in IFU)**
> 2008
> Difficulty urinating Pain
> Scarring
> Mesh Exposure requiring treatment
> 2011
> Mesh exposure into the vaginal canal
> Mesh exposure associated with pain during intercourse for the patient and partner
> Mesh exposure which may require removal of exposed mesh in office or operating room
> 2012
> Pelvic Pain
> Development of Urinary Incontinence
> Voiding Difficulties

[191] ETH.MESH.04094863 (e-mail from Dr. Meng Chen to Bryan Lisa, Jan. 29, 2009).
[192] ETH.MESH.01239065 at 9066 (July 14, 2009 email from Aaron Kirkemo MD to Piet Hinoul MD and David Robinson MD).
[193] *Id*.
[194] *Id*.

Hemorrhage or hematoma
Urinary tract infection
Wound healing problems
Injury to ureters
Pelvic abscess formation
Risk of infection
Vaginal scarring
Mesh contracture (mesh shortening due to scar tissue)

Some of these risks have been disclosed in Ethicon's other PROLENE mesh IFUs. For example, Ethicon's IFU for PROLENE hernia mesh states as follows: "The use of PROLENE Mesh in contaminated wounds should be with the understanding that subsequent infection may require removal of the material."[195]

Even though Ethicon changed its Patient Brochures in 2011 and 2012 to include additional significant adverse events/risks, it never added the same information to the TVT-O IFU. This is true despite the fact that Ethicon had internal discussions about updating the IFU in 2009 after the 2008 FDA Public Health Notification (PHN). Specifically, a meeting was held to decide, among other issues, whether to update "the current Adverse Reaction of tape exposure and post-operative dyspareunia in the TVT-family products…."[196]

After discussing the 2008 PHN, competitors' labels and Remetrex issues, impressions were that tape exposure/erosion/extrusion were very frequently reported, patients did not feel there were adequate pre-op consent or risk-benefit assessment, patient specific concerns about exposure/erosion/extrusion, incontinence recurrence, post-operative dyspareunia and pain-affect quality of live and affect daily routine, re-operations and post-operative complications disproportionate to pre-operative-consent-expectations.[197] Despite these discussions and Ethicon's scientific knowledge of these serious, devastating and life-changing adverse events/risks, to this

[195] ETH.MESH.02342102.
[196] ETH.MESH 04081189.
[197] *Id*.

day, it has never updated or changed its IFU to include this information.

Repeatedly, the reason given for not updating an IFU to make it more accurate and safer that doing so would threaten the launch timing of a new product. For example, when discussing the IFU for TVT-Exact, Dr. David Robinson cautioned against making too many changes from the original TVT-R IFU: "Just to clarify… the more changes we make to the IFU that differ from TVT-Classic, the higher the risk will be to the submission timing."[198]

In summary, Ethicon did not fully inform physicians about numerous adverse reactions/risks associated with the TVT-O despite the fact that Ethicon had scientific knowledge of the risks from the time the product was first sold. As a result, physicians were unable to fully consent and inform patients of the risk associated with TVT-O. In addition, some risks included by Ethicon in the IFU are mischaracterized to minimize the actual risk. Finally, when given numerous opportunities to update the IFU, and in the face of specific requests to do so from numerous medical professionals, Ethicon did not make the necessary updates. To a reasonable degree of medical certainty, this prevented physicians and patients the ability to make an informed choice regarding the use of the TVT-O. For a surgeon to properly inform the patient of all the known risks involved in any procedure involving an implantable medical device, the surgeon relies upon the manufacturer to have scientific knowledge of and convey all characteristics of its products that could impact safety and efficacy. Specifically, surgeons rely on the "Adverse Events/Risks" section of a medical device IFU to gain scientific knowledge regarding adverse events or undesirable effects that the company knows are associated with the product.

5. At Launch of TVT-O, Ethicon Cut Funding for Training.

[198] ETH.MESH.10632650 at 10632652.

Another way in which Ethicon could inform physicians about safety issues with TVT-O was through Professional Education or training. Proper training was recognized as a prerequisite to safe use of the TVT-O. I understand this from having personally attended a training session with Dr. de Leval in Leige, Belgium in 2004. For example, in the original design documents for the TVT-O, Ethicon recognized that training of physicians was necessary and required: "Is special training needed for the safe and effective use of the device? "Yes".[199] In fact, many of the Ethicon employees in charge of developing the TVT-O assumed training would be required. Brian Luscombe, a marketing lead, wrote: "[W]e should not expect them to be able to do the procedure just by reading the IFU, since we do require formal training as well."[200] Dan Smith wrote: "I thought we required training prior to sale!"[201] In fact, prior to the launch of TVT-O, Ethicon insisted its sales representatives not train physicians but that they attend formal training:

> By having your physician "formally" trained, it minimizes the potential for legal liability for all parties involved: the practicing physician, the company representative, and the company. It is a GYNECARE policy that a representative should not be the sole trainer of a physician on the procedures involving GYNECARE TVT.[202]

In answer to inquiries from journalists about its "requirement" for training, Ethicon claimed it was unique and it set the company above the competition on issues of patient safety. In a September 5, 2003 e-mail exchange, 4 months before the launch of TVT-O, an Ethicon employee wrote:

> Providing physician training is a very expensive proposition, however, since our business practices are guided by our CREDO, we believe in doing the right things for patients and our customers…. We still require that the physician attend a GYNECARE sponsored Professional Education event with one of our

[199] ETH.MESH.00259047 at 9431.
[200] ETH.MESH.00864085 at 4086 (email Brian Luscombe to Dan Smith and Janice Burns, et al).
[201] ETH.MESH.06880021.
[202] ETH.MESH00030098.

preceptors…."[203]

However, as discussed above, in the later part of 2003, Ethicon was losing significant market share due to the competition's trans-obturator devices. Because of this business loss, in the very year the TVT-O was launched, Ethicon severely cut spending on professional education and training. An August 27, 2004, e-mail states as follows:

> Because the GYNECARE business is tracking behind the Original Business Plan, the marketing spend needed to be reduced in order to deliver the committed profits…. [This] will limit the Professional Education events that can be done….[204]

By April 2005 the funding for Professional Education was cut even more: "You know we are all trying to get more funding, right now we do not have anything…."[205] Without the funds to do formal training, Ethicon recommended to its sales representatives that they train physicians: "To me the biggest progress we can make is to reinforce the reps in "training" themselves on TVT-O, specially the "average" obgyns: they can sit down with them for 45 minutes, go through the procedure (cd rom and leaflets), discuss the anatomy and use a sample on a PF model…. The more we improve our ProfEd processes and ways of thinking, the more we will increase our ROI, the more money we will get: logic and discipline, right?"[206] This contrasted sharply with Ethicon's CREDO / "patient centric" policy of two years earlier. Not only did physicians have an inadequate and inaccurate IFU, now they were not being provided with any training to correct those deficiencies. For example, when Dr. Meng Chen was seeing what she described as a "surge" of bladder perforation complaints, she recognized that, although bladder perforation was in the IFU, Ethicon should consider initiating better training:

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[203] ETH.MESH.03738468.
[204] ETH.MESH.05795299.
[205] ETH.MESH.05795322 at 5323.
[206] ETH.MESH.05795322 at 5324.

> I see a string of bladder/urethra perforations with sling procedures using various TVT devices (A, O, S). Although most of these ended up not reportable as only catherterization was performed, I see there is a 'surge' of such events. The IFUs do address potential bladder injury specifically. But a retraining process may be necessary?.... I do not feel it is a good trend for these perfs.[207]

But, as shown above, by this time, Ethicon had cut the funding for training "in order to deliver the committed profits."[208]

I. The TVT-O Device Is Not Designed for Special Patient Populations Nor Does the IFU or Marketing Inform Physicians or These Patients of Poorer Outcomes or Higher Risks.

Ethicon promoted the TVT-O as a "reproducible" technique that was appropriate for all patients. For example, Ethicon instructed its sales force to specifically target physicians to use the TVT and TVT-O in obese patients.[209] However, as Ethicon's Medical Director, Dr. Kirkemo, testified obese patients do not fare well with these devices.

> Q. One of the things that was actually shown in the TVT World study that you worked on was that for obese patients, for example, the efficacy was significantly down when slings were used in obese patients; is that correct?
> A. Obese people tend -- not to do as well.

In fact, Ethicon's study showed obese patients had about one half the success of those patients who were not obese. In addition, as Dr. Kirkemo testified, obese women suffered from more complications: "Their chance of success goes down. Their risk of complications goes up."[210]

Yet, Ethicon did not put this critical information into the IFU. Dr. Kirkemo testified:

> Q. Did you ever put that in the IFU?
> A. No….[211]

Not only did Ethicon not put this critical information in the IFU, Ethicon also did not inform

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[207] ETH.MESH.04090122 (10/12/07 email from Dr. Meng Chen to Carolyn Brennan).
[208] ETH.MESH.05795299.
[209] See, e.g., ETH.MESH.00640394 (trying to convince physicians to use TVT-O on obese patients); ETH.MESH.05119622 at 9623 (TVT "is a good choice for the obese patient or elderly patient….").
[210] Kirkemo Dep. (1/7/2014) 556:24-557:1.
[211] Kirkemo Dep. (1/7/2014) 556:4-19.

patients:

Q. Did you ever tell patients that in a single patient brochure, that if they were obese, their chances of this being successful were less than half?
A. We did not.[212]

Ethicon also did not include information in its IFU about how the TVT-O had less efficacy and higher risk for older women or younger, active women.

Q. Did you -- you also learned in the TVT World study, or maybe you knew this before, too, that being elderly decreased, or being very young, in fact, decreased the efficacy of the Ethicon sling procedures; correct?
A. With any incontinence operation, old people tend not to, you know, do as well.
Q. And was that ever put in a patient brochure or communicated to patients as far as you know?
A. As near as I can tell, in any marketing document, no.
Q. And what about the very young or the younger women; that was shown in TVT World that even younger women had lower efficacy; correct?
A. Some women that are very, very active can -- and have ISD can overcome the effect of the sling.
Q. In other words, the sling can fail.
A. The sling can be less than a hundred percent effective.
Q. And that was never actually communicated to patients as far as you know, correct, by Ethicon?
A: To my knowledge, no.
Q. And neither the older women or the younger women in issue we were just talking about, neither of those are included in the IFU; correct?
A: Those specific things are not mentioned.[213]

The TVT-O inventor, Professor de Leval discussed the fact that the TVT-O was inappropriate for treatment in younger active women.[214] However, physicians and patients were not informed of this defect, nor was the TVT-O modified to correct it.

Ethicon also did not inform physicians and patients that the TVT devices, including the TVT-O would not work as well and would be more dangerous for women who smoked or who had Diabetes – a very large percentage of the patients to whom TVT was being marketed:

[212] Kirkemo Dep. (1/7/2014) 557:5-557:9.
[213] Kirkemo Dep. (1/7/2014) 557:10-558:21.
[214] ETH.MESH.04050265 ("The second source of pain comes from the presence of the tape in the adductors…. This is of specific importance in young, active and/or sportive patients.").

Q. Smoking decreases the efficacy of slings; correct?
A. Yes.
Q. Diabetes decreases the efficacy of slings; correct?
A. It can because you have neurologic, you know, disease.
Q. Neither smoking nor diabetes is listed as a potential contraindication or something special to look for in the IFU; correct?
A. It is not listed in the IFU….
Q. And Ethicon never communicated to patients that smoking would increase their risk of adverse outcomes or decrease the chance that the sling would work; correct?
A: We did not.
Q. And the same with diabetes. Ethicon never communicated to patients when they were selling TVT devices that diabetes would decrease the chance that the device would work or increase the chance that they would have an adverse event; correct?
A. I did not see that, no.

In addition, Ethicon promoted the TVT-O as a "one-sized fits all" device. However, because of the unique fixed radius and size of the TVT-O the helical passer and its passage, this was not accurate. For example, one anatomical study of the obturator foramen demonstrated significant variation of the bony architecture.[215] This could impact the trajectory of the TVT-O needles (trocars) directing them into areas within the pelvis with a higher density of blood vessels and nerves. The conclusion was that women, especially women with small obturator foramen, are at higher risk for neurovascular injury with the TVT-O procedure.[216] This was something that de

[215] Ridgeway, B., et al., *Variation of the obturator foramen and pubic arch of the female bony pelvis,* Am J Obstet Gynecol. 2008 May, 198(5):546.e1-4; Spinsosa, J., et al., *Transobturator surgery for female stress incontinence: a comparative anatomical study of outside-in vs inside-out techniques*, BJU Int. 2007 Nov, 100(5):1097-102, Epub 2007 Sep 14; Hinoul, P., et al., *Anatomical variability in the trajectory of the inside-out transobturator vaginal tape technique (TVT-O)*, Int Urogynecol J Pelvic Floor Dysfunction 2007, 18:1201-6; Atassi, Z., et al., *Haemorrhage and nerve damage as complications of TVT-O procedure: case report and literature review*, Arch Gynecol Obstet 2008, 277:161–4, Boyles, S., et al., *Complications associated with transobturator sling*, Int Urogynecol J 2007, 18: 19–22; Zumbe, J., *Obturator and thigh abscess after transobturator tape implantation for stress urinary incontinence*, Urol Int. 2008, 81: 483-485; ETH.MESH.02019485 (knowledge of variable obturator foramen anatomy); Zahn, C., et al., *Anatomic comparison of two transobturator tape procedures*, Obstet Gynecol 2007, 109:701-6; Laurikainen, E., et al., *Retropubic Compared with Transobturator Tape Placement in Treatment of Urinary Incontinence*, Obstectrics & Gynecology, Vol. 109, No.1, Jan. 2007 ("The number of patients complaining of postoperative groin pain was significantly greater in the TVT-O group than in the TVT group, 21 (16%) compared with 2 (1.5%)…. " "[T]he groin pain of the TVT-O patients persisted for 2 weeks in ten patients, for 4 weeks in three patients, and for 2 months in one patient, the rest having pain for a few days.").
[216] *Id.*

Leval and Ethicon senior personnel discussed within months of the launch of the TVT-O. On March 22, 2004, three months after launch, Ethicon senior personnel held a "confidential meeting" with Professor de Leval to discuss "possible modifications of TVT-O."[217] One modification was to the diameter of the passers to account for the smaller pelvic region in Asian women.[218] This was raised as a concern nearly a year before launch by Professor Ulmsten: "He is concerned about ETHNICITY – i.e., does the arc of the devices and surgical technique translate to black or Asian population as they have anatomically diverse anatomical relationships between urethral meatus and position of the obturator. Are we sure that the device will work in all patients in the same safe way?"[219] Yet, Ethicon did not to make any modifications to the TVT-O to enhance patient safety related to this issue in part because, as de Leval stated in his memo, the potential of "criticisms of the competitors."[220] Nor did Ethicon warn physicians or patients about these risks.

Accordingly, it is my opinion to a reasonable degree of medical certainty that the TVT-O as designed is not effective for special patient populations. In addition, the TVT-O is dangerous and can cause significant, lifelong injury due in part to its "one-size fits all" design. Moreover, Ethicon failed to inform physicians of the importance of these patient variations (particularly with use of the TVT-O device and the fixed radius of the helical passer) and the potential for permanent, serious injury from the TVT-O. Because Ethicon failed to inform physicians, Ethicon also removed the ability of the physicians to fully inform patients of these risks.

J. Ethicon failed to reveal material facts about complications and conflict of interests regarding data promoted in the materials.

[217] ETH.MESH.02180759.
[218] *Id.* at 3 ("Designing and manufacturing of passers having a shorter dimeter (5-5.5 cms) for Asian patients.").
[219] ETH.MESH.06884249.
[220] *Id.*

Since the TVT was first launched, Ethicon has sent materials in various forms to physicians promoting long term follow up data on the original cohort of patients implanted with the TVT from 1995-1996.[221] Ethicon continued to cite to this data in its TVT-O materials.[222] In addition, the materials tout low complication rates related to various adverse reactions, including erosions. These materials include press releases, marketing brochures and email blasts.

The long term data primarily relied on by Ethicon throughout these materials relates to the Ulmsten/Nillson studies. These studies were originally started by Dr. Ulmsten, the inventor of the TVT, and continued by Dr. Nillson after Dr. Ulmsten's death. Prior to selling the TVT to Johnson & Johnson, Dr. Ulmsten owned a company called Medscand. As discussed more fully below, Johnson & Johnson hired Dr. Ulmsten and Medscand to conduct studies related to the TVT. To this day, Ethicon relies heavily on these studies and uses them in numerous promotional materials despite the fact that Ethicon never disclosed to physicians the potential conflict of interest and inherent bias that exists due to Dr. Ulmsten's relationship with Ethicon and Johnson & Johnson. In addition, Ethicon never disclosed to physicians that the device used in the original Medscand study was different than the TVT device. It is important to physicians using the TVT that the data in these types of promotional materials is accurate, unbiased and that physicians are informed about any potential conflicts of interest in the data contained within the materials. In other words, physicians rely on Ethicon to provide fair and balanced information and to ensure that physician have been given all the data and not just the positive press release data.

Despite using the Ulmsten data to promote the TVT, Ethicon never disclosed to

[221] ETH.MESH.0015598,; ETH.MESH.00658058,;ETH.MESH.01186068; ETH.MESH.02236784; ETH.MESH.02237103; ETH.MESH.03459211; ETH.MESH.05183409; ETH.MESH.00339437; ETH.MESH.05794787.
[222] ETH.MESH.00163582.

physicians the bias and inherent conflict of interest related to the Ulmsten data. Specifically, in its promotional materials, Ethicon (Johnson and Johnson) never informed physicians about its relationship and contracts with Professor Ulmsten and his company Medscand. It is clear from the contracts that the publications and data from Dr. Ulmsten where contracted for hire by Johnson and Johnson International.[223]

The License and Supply Agreement between Johnson and Johnson International and Medscand (Ulmsten's Company) dated February 13, 1997, states in section 3.6 Milestone Payments:

> Johnson and Johnson International (JJI) shall pay shall pay to Medscand the following payments (b). A payment in the amount of $400,000.00 due on February 28, 1997; provided, however, that in the event that Clinical Trials as specified in Exhibit C have not been completed by such date, then such amount shall not be due until the completion of the Clinical Trials.[224]

Under Exhibit F, Consulting Agreement with Professor Alf Ivar Ulmsten, section 4 Confidential Information Rights to Inventions and Copyrights (B) it states:

> any copyrightable work whether published or unpublished created by supplier Dr. Ulmsten directly as a result of or during the performance of services herein shall be considered a work made for hire, to the fullest extent permitted by law and all rights, titles and interest herein, including worldwide copyrights shall be the property of the company as the employer and party specially commissioned said work.[225]
>
> Finally, in Exhibit C, Clinical Trials, it states:
>
> the results of clinical trials will be considered acceptable if, first, they do not differ significantly from the results published in the original article published in the Int. Urogynecol J 1996-7:81-86 by U. Ulmsten, et.al., with regards to the following items: Safety 1.1, preoperative complications 1.2 , post operative complications 1 year from operation 2. Efficacy. Second Long term results over 1 year from operation do not show a deterioration of rates significantly different from those of the standard suburethral slingplasties. It is assumed that from 12 –

[223] ETH.MESH.08696085 at 6085-6134.
[224] ETH.MESH.08696091.
[225] ETH.MESH.08696116.

> 60 months a gradual decrease in efficacy of 5% is normal. 3. No significant numbers of unexpected i.e. not addressed in the original article published in the Int. Urogynecol J 19967 81-86 by U.Ulmsten at et.al. procedure related i.e. not addressed in the review article published in the Int. Urogynecol J 19945: 228-239 by G. N. Ghomiem et.al. complications appear at any time in the postoperative course.[226]

In total, Dr. Ulmsten stood to gain millions of dollars for the 6 papers that he published on the TVT device. In addition, the results of those studies would be found acceptable for payment only if they did not differ from the parameters sent by Johnson & Johnson regarding complications and efficacy. The Ulmsten studies have an inherent conflict of interest and bias as they were "made for hire" and standards were set by Johnson & Johnson. As set forth above, if Dr. Ulmsten did not meet the standards set forth by Johnson & Johnson, he did not receive substantial payments for the "studies." As a result of this relationship, there is a clear conflict of interest and potential for enormous bias issues.

The conflict of interest and bias created by the relationship between Ethicon and Dr. Ulmsten was acknowledged by Dr. Axel Arnaud, Ethicon's European Medical Director, in a recent deposition. Specifically, Dr. Arnaud testified that such an agreement like the one discussed above between Dr. Ulmsten and Johnson & Johnson creates a potential conflict of interest.[227] Dr. Arnaud also acknowledged that when Johnson & Johnson enters into this type of agreement with a physician or his company and the study is published, there "certainly" needs to be a disclosure of the relationship.[228] Additionally, Former Ethicon Medical Director, Dr. David Robinson, testified that in his experience working in the industry for medical device manufacturers, it is best that potential biases be disclosed.[229] He also testified that if publications

[226] ETH.MESH.08696132.
[227] Arnaud Dep. (7/20/13) 497:24-501:21, 509:8-17.
[228] Arnaud Dep. (7/20/13) 514:17-515:1.
[229] Robinson Dep. (9/11/13) 214:15-21.

from somebody like Ulmsten or Nilsson about safety and efficacy are being published, it is best if they disclose that they have a financial bias or conflict of interest.[230] In fact, in an April 2009 email exchange with Medical Director Piet Hinoul about a physician who, like Ulmsten, is a consultant and inventor for competitor Boston Scientific, Dr. Robinson states that that situation presents "enormous bias issues."[231] Despite two of its medical directors testifying that the relationship between Ulmsten and carried over to Nilsson presents a conflict of interest and bias, Ethicon has never disclosed this information in its promotional pieces. This is information physicians and patients have a right to know so that a proper informed decision regarding the value of the data in the studies and the use of the product can be made.

Aside from never disclosing to physicians the underlying conflict of interest and bias of the Ulmsten studies in its promotional pieces, Ethicon also never informed them about other problems with the data, including incomplete data on the original cohort, data incorrectly reported and erosion rates underreported. In the original 510k submission for TVT Classic, Ethicon used Medscand data from the Scandinavian Multicenter Study.[232] The report shows that 12 month follow was obtained for 90 of the original 131 patients, without explanation of why there was a loss of 41 patients from the study. The study also describes a complication of wound infection: "while the vaginal infection required surgical intervention with resection of exposed mesh." This represents a vaginal mesh erosion/extrusion/ exposure and needs to be reported as such. However, when the paper was published (Ulmsten, Int Urogynecol J 1998), the paper states that there was no defect healing and no tape rejections. It further misrepresents the outcome for this patient as "The patient with the wound infection had vaginal atrophy. After minimal vaginal

[230] Robinson Dep. (9/11/12) 215:8-13.
[231] ETH.MESH.03259439; Robinson Dep. (9/11/13) 219:6-220:10.
[232] ETH.MESH 00371587.

wall resection and effective local estrogen treatment she healed without further intervention. There was no tape rejection."

If Ulmsten had reported a mesh erosion/extrusion/exposure with mesh excision in his study, it would not have been acceptable under Exhibit C of his consulting contract for payment of the $400,000.[233] This demonstrates that the results of this paper were potentially biased by the payment Ulmsten would receive for favorable data and should discount the data. At the very least, Ethicon should have informed physicians about the relationship between Ethicon and the Ulmsten studies.

Many of the marketing brochures tout the "[t]he urethral erosion rate less than or equal to that of traditional slings; no reported urethral erosions in 10 studies of 50+ patients."[234] The reference used for the first part of this statement is from Dr. Gary Leach) who looked at traditional sling procedures done before 1993, when traditional slings were performed at the bladder neck and purposely placed under tension to treat severe stress urinary incontinence from intrinsic sphincter deficiency (particularly among Urogynecologists).

The second part of this statement regarding "no uretheral erosions" is incorrect. In published studies, Dr. Karram found one case of urethral erosion in his study of 350 Gynecare TVTs performed (Karram Obstet Gynecol 2003) and Hammad found nine cases of urethral erosion in his study (Hammad Eur Urol 2005).[235] His study followed the complications of 1459 patients 993 of whom had Gynecare TVT, while the remainder has SPARC procedures. While the authors do not break down the incidence of urethral erosion by product, it is exceedingly unlikely that all erosions happen in the SPARC group.

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[233] ETH.MESH 08696132.
[234] ETH.MESH 00339439.
[235] Karram, M.M., et al., *Complications and untoward effects of the tension-free vaginal tape procedure*, Ob & Gyn 2003, 101:929-32.

The statement regarding "no uretheral erosions" also did not include deTayrac's 2003 paper of 61 patients (31 TVTs) which showed a 3% urethral erosion rate.[236] Dr. Shlomo Raz described a study of 26 patients who presented with voiding dysfunction, including symptoms of severe urethral, pelvic and genital pain, urinary retention, recurrent UTIs, de-novo urgency with urge incontinence found to have mesh from a sling procedure in the bladder or urethra.[237] Their patients were found to have been treated conservatively with anticholinergic medication. They conclude that "dysfunctional voiding symptoms after sling procedure should elicit a high degree of suspicion if pharmacotherapy is not successful in alleviating symptoms...Cystoscopy should be considered if the patient remains symptomatic despite pharmacotherapy."

In one of the Nilsson studies, Dr. Nilsson describes four patients on "anticolinergics" (Int Urogynecol J 2008 Table 3). They conclude: "It is also encouraging to see that no late adverse effects of the polypropylene tape material was found and that erosion of the tape into adjacent tissue did not occur." However, this statement cannot be made for 4 patients who are on pharmacotherapy without a cystoscopy, which was not performed in the 11 year follow-up study. Dr. Raz's review of the literature found multiple cases of urethral erosions in a large series with TVT.[238] There have also been multiple case reports attesting to the fact that urethral erosion does occur specifically with Gynecare TVT products.[239] To imply that urethal erosion does not occur is not giving physicians fair and balanced information about the true incidence of urethral

[236] de Tayrac, R., et al, *A prospective randomized trial comparing tension-free vaginal tape for surgical treatment of stress urinary incontinence*, Am J Obstet Gynecol 2004, 190:602-8.
[237] Deng D.Y., et al., *Presentation and management of major complications of midurethral slings: Are complications under reported*, Neurourology Urodynamics 2007, 26:46-52.
[238] Karram 2003, Hammad 2005.
[239] Sweat, S., et al, *Polypropylene Mesh Tape for Stress Urinary Incontinence: Complication of Urethral Erosion and Outlet Obstruction*, J Urology 2002, 168:144-146; Gerstenbluth, R.E., et al, *Simultaneous Urethral Erosion of Tension-Free Vaginal Tape and Woven Polyester Pubovaginal Sling*, J Urol. 2003, (2 Pt 1) 170:525-6; Vassallo, B.J.., et al., *Management of latrogenic Vaginal Constriction*, Am J Obstet Gynecol 2003, 102(3):512-20; Haferkamp, A., et al., *Urethral Erosion of Tension-Free Vaginal Tape*, J Urol 2002, 167(1): 250.

erosions with TVT products.

Later, Nilsson publishes the 5 year follow-up of this cohort.[240] He describes the cohort: "a prospective open multicenter trial was conducted in the Nordic countries at the beginning of 1995. The short-term results were published in 1998." This implies that these are the same patients as published in 1998. It is interesting or an incredible coincidence that the exact number of patients receiving 12 months of follow-up in the Medscand publication (90) was the exact number being described in the 5 year study. There is again no mention of the outcome of the other 41 patients from the original cohort. Another interesting detail in the 5 year study is that the original number of centers used for the study (6) was now down to 3, again without explanation. The 5 year report does describe the original patient with the wound infection but again fails to mention she had mesh excised, "1 case (1.1%) of infection of operating site was observed."

In 2006, Dr. Nilsson published a different study on long term outcome of patients with TVT.[241] He describes his new patient population: "A multi-center study comprising only carefully selected primary cases revealed a promising cure rate of 85% after 5 years (reference his 5 year study) and 81% at 7 years."[242] These two papers are the subject of many press releases and marketing brochures, but they never described that these were carefully selected patients. "To our knowledge, the long-term effect and effectiveness of the TVT procedure has not yet been studied in an unselected patient group. We earlier reported 16-month follow-up results of a general patient group referred to a tertiary medical unit and comprising primary, recurrent, mixed, and low pressure urethra cases. In the present study, we report the long-term results in the

[240] Ulmsten data; Nilsson, Int Urogynecol J 2001.
[241] Kuuva , N., et al., *Long-term results of the tension-free vaginal tape operation in an unselected group of 129 stress incontinent women*, Acta Obstetricia Gynecologica Scandanavica 2006, 85:4 482-87.
[242] Nilsson, Obstet Gynecol 2004.

same above-mentioned group." They describe a 3.1% mesh "visualized" rate, half of which needed surgical resection. These results, more representative of what one would see in a normal practice, is never mentioned in press releases or marketing documents.

Conversely, when Ethicon receives adverse information, it does not make it into the promotional pieces. Dr. AC Wang's abstract, "Tension-Free Vaginal Tape (TVT) for Urinary Stress Incontinence - A Preliminary Report" was used in the original 510k submission in October of 1997 as support for FDA clearance of the TVT.[243] However, when Dr. Wang reported that he had 25 cases of "failure of vaginal healing considered by him to be potential tape rejection...in each case the revision failed within 2 weeks, requiring further surgery to excise mesh and repair the vaginal wound," this important information never made it into the marketing materials or press releases.[244]

The long-term follow-up data (Ulmsten/Nillson data) used by Ethicon to promote the lack of risk of TVT and TVT-O is spurious at best. We have incomplete data on the original cohort, data that is falsely reported, original sites that were excluded without explanation and a lead investigator who had a significant relationship and financial incentive to reach certain results with the data. This is the same data which is now used repeatedly in promotional and marketing materials sent to physicians.

This creation of unreliable data continued during the development of TVT-O. The first paper on TVT-O was published by de Leval in November 2003, 2 months before launch.[245] De Leval reports on the results of 107 patients implanted with the TVT-O. The problems with the paper are extensive and material:

[243] ETH.MESH.00371551.
[244] ETH.MESH.00409675.
[245] ETH.MESH.06880472 (Ex. T-522).

1) De Leval does not disclose his financial interest in the TVT-O.[246]
2) De Leval does not disclose his relationship with Ethicon.
3) It is not disclosed that Ethicon paid for most of the study to be done.
4) It is not disclosed that Ethicon materially participated in the drafting of the paper.
5) It is not disclosed that Ethicon's clinical specialist concluded that de Leval and his hospital had acted illegally, failed to get proper consent or regulatory approval.[247]

In fact, despite multiple requests to see the data supporting this study, Ethicon never reviewed it. This was in large part because it was not captured correctly.[248]

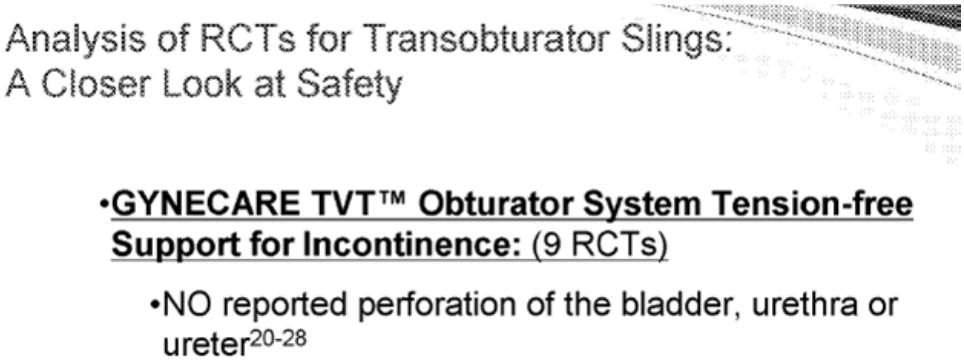
Ethicon's promotional materials suffer from innumerable other inaccuracies and misstatements. In many promotional materials Ethicon states that randomized controlled clinical trials are the highest rated type of trial that provide the most validity.[249] Various marketing pieces go on to state that both TVT and TVTO have the most Level 1 evidence supporting the safety and efficacy of the mesh. For example, one piece claims "Here we've looked at **all** RCTs for Gynecare TVT Obturator and AMS Monarch and have found a better safety profile for GYNECARE TVT Obturator." It continues: "GYNECARE TVT Obturator has 9 RCTs studying outcomes in over 600 patients. In this group there were no reported perforations of the bladder, urethra or ureter."[250] However, Ethicon excluded from this statement one of the primary studies on the safety and efficacy of the TVT-O -- the Laurikainen study. In this RCT, there was a 2.3% vaginal perforation rate and a 16% pain rate. This study was not included in the marketing documents promoting the TVT-O even though it was an RCT and was available at the time. In other marketing and education materials, Ethicon does include the Laurikainen study as an RCT; hence, Ethicon had the scientific knowledge and data from this

[246] ETH.MESH.03918253 (Ex. T-502).
[247] ETH.MESH.03934952 (Ex. T-499).
[248] ETH.MESH.01808311
[249] ETH.MESH.03965159.
[250] *Id.*

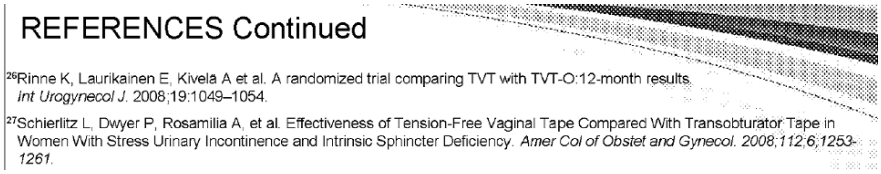
study.[251]

2007 (January – July)	Meschia et al	Neuman	Laurikainen Et al
Urinary tract infection	0	0	13%
Wound infection	0	0	0
De Novo Urge	?	3,3%	2,3%
Pain	5%	-	16%

Perhaps the most misleading aspect of the claims related to the "9 RCTs" is that one of the "9 RCTs" that Ethicon relies upon to support the safety of the TVT-O did not even use the TVT-O device, but its competitor. For example, the below marketing piece cites to 9 RCTs listed as references 20-28.



Cite 27 of this marketing piece that was presented to physicians is the Schierlitz study:



[251] ETH.MESH.04049320.

This study that is cited in many marketing, promotional and educational pieces, did not even use the TVT-O device. Below is an excerpt from the study that explains what devices were used:

scribed by Ulmsten.[12] The transobturator tape procedure was performed with the Monarc subfascial hammock system (American Medical Systems, Inc., Minnetonka, MN) using the technique described by the manufacturer. Cystoscopy was used routinely to

The statements that the 9 RCTs demonstrate the safety of the TVT-O device appeared as far back as 2008 and continued on materials as recently as 2012.[252] Including this study as support for the safety and efficacy of the TVT-O procedure was misleading at best.

K. Ethicon's Patient Brochures misstate information regarding complications and success rates and lack fair balance.

In its TVT-O patient brochures, Ethicon routinely represented to patients and physicians that the success rate of the TVT device was between 97 and 98%. These claims are based on the 5 year, 7 year, and 11 year follow-up to the Ulmsten/Nilsson study. What is not adequately explained to patients is that this "success rate" is a combination of patients who are "cured" and those who are considered "improved," a fact that is not disclosed in advertisements directed at patients, but is generally disclosed in advertisements directed at doctors. Further, Ethicon does not disclose to patients or physicians that the numerous authors of this study on which Ethicon has made the cornerstone of its marketing program are paid consultants of Ethicon, including, Dr. Ulmsten, Dr. Nilsson, Dr. Falconer, and Dr. Rezapour.[253] Ethicon also does not inform patients of the existence of other long-term studies which show a much lower success rate for TVT.

Ethicon's Patient brochures tells patients that 98% of women treated with the Gynecare

[252] ETH.MESH.08376560
[253] ETH.MESH.09746615; ETH.MESH.09748842; ETH.MESH.09748848; ETH.MESH.08696050; ETH.MESH.08167644.

TVT are still dry or report significantly less leakage after 7 years.[254] This claim is combined with an assertion that the TVT is trusted by over 1 million women. This claim undoubtedly gives women the false impression that this claim of 98% "success" with TVT is based on all of the more than 1 million women who have been treated with TVT, when in fact this statement is based on a single study of 90 patients, only 80 of whom were available for follow-up after 7 years.[255] The brochure also does not tell patients that the actual cure rate in this study was only 81.3% with the TVT until page 7 of the brochure, and then only in fine print at the bottom of the brochure. The brochure also does not inform patients of the criteria for a patient to be considered "significantly improved." Further, patients were not informed that 8% of these 80 patients felt their incontinence had become worse between their 5 year evaluation, and the 7 year evaluation that was the basis of this study. Further Ethicon knew of other studies showing a much lower success rate than the single 90 patient study they had elected to feature in their patient brochures. For example one study found only a 63% success rate after only two years, and that study was sponsored by Ethicon and was a randomized controlled trial (RCT), a study type known to produce the highest quality evidence.[256] Yet Ethicon chose not to share that information with patients. By not presenting patients with an overview of the likely success rates with TVT and instead of selecting a single study which happened to have a high apparent success rate when the "substantially improved" patients were included as a success, Ethicon failed to include fairly balanced material in their brochure.

This same patient brochure also informs women who are considering having TVT

[254] ETH.MESH .00163583.
[255] Nilsson, C.G.. et. al., *Seven year follow-up of the Tension –Free Vaginal Tape procedure for treatment of urinary incontinence*, Ob & Gyn 2004, 104: S5-S8.
[256] Ward, K., et. al., *Prospective multicentre randomized trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence*, BMJ 2002, 325:1-7.

surgery that "few women experience complications"[257] This is a clear misrepresentation of data and complication rates known to Ethicon and the scientific community. For example, in one two- year study, 39% of the patients who received a TVT device experienced a least one complication. In fact, Ethicon's medical director, Dr. Weisberg testified that he knew bladder perforations with TVT occurred in 2 to 3 percent of patients ranging up to 19 percent in some populations.[258] In 2002, Ethicon was also aware of a report of 25 wound healing defects out of approximately 600 patients – all were suspected to be tape rejections by a very experienced TVT surgeon. This would represent an erosion rate of slightly over 4% seen in these 600 patients.[259] The Barber study found an erosion rate in patients receiving the TVT device of between 5 and 6%,[260] a rate consistent with what the President of Ethicon, Renee Selman, believed to be the overall rate of erosions seen with the TVT ("between five and ten percent"). The complication rates known to Ethicon are not consistent with the claim in its patient brochures that few women experience complications, and grossly understate the risk to women deciding whether or not to have the procedure.[261]

Some patient brochures also contain statements and taglines that further give the patient the false impression that complications are rare, and minimize the invasiveness, recovery time and potential complications with the procedure. For example, tag lines like "[s]top hoping, start living," and "[o]ne day you have stress urinary incontinence, the next day you don't- end of story,"[262] mislead patients into thinking that they will never again have to deal with the

[257] ETH.MESH 00163583.
[258] Weisberg Dep. (5/ 31/13) 422:20-423:1.
[259] Id. at 434:1-437:25; ETH.MESH.00409674.
[260] Barber, et al., *Transobturator tape compared with tension-free vaginal tape for the treatment of stress urinary incontinence*, Obstet Gynecol 2008, 111:611-621.
[261] Selman Dep. (6/21/13) 583:17-584:17.
[262] ETH.MESH.08003263.

symptoms of stress urinary incontinence or other urinary symptoms when the clinical studies show that anywhere between 19% and 37% of patents in clinical studies still have some stress urinary symptoms after treatment with TVT. Further, it minimizes the patients' consideration of the possibility that they may have new symptoms to manage as a result of their operation, including but not limited to potential recurrent urinary tract infections, new urge incontinence, dyspareunia, chronic pain, erosions, and urinary retention.

Other statements in the brochure give women a false impression of the recovery time. "Recovery is quick,"[263] and "Short recovery period and quick return to normal activities,"[264] give patients a false impression of the actual recovery time involved. It is not unusual for women to take 4 weeks or longer before they can safely return to work after the TVT-O procedure, particularly in jobs that require physical exertion as part of the job functions. One patient brochure states: "Low incidence of reported serious complications (<0.04%)."[265] However, as discussed above, more than one in four women will suffer from groin, thigh, or nerve pain after TVT-O – something that is not disclosed in any patient brochure.

Further, the recovery time varies from patient to patient, with some patients taking 8 weeks or even longer to completely heal and return to normal activities.

L. Post-Marketing Adverse Events

Ethicon did not actively try to determine how many patients were hurt by its devices, including the TVT-O, or how severely they were hurt. Instead, Ethicon had a "passive" system of measuring how many and what type of adverse events the TVT-O was causing. Ethicon's Director of Post-Marketing Surveillance testified that this type of passive collecting of reports

[263] ETH.MESH.08003291.
[264] ETH.MESH.08003264.
[265] ETH.MESH.00658454 (citing to "Data on File").

understates how many people are actually being hurt by its devices:

> THE WITNESS: So we -- from a reactive perspective for complaints, we can only process the complaints that are reported to us, so -- and as we discussed earlier, they come from many different avenues; but again, they're reactive in nature, which means we are processing what is given to us or reported to us.
> ….
> Q. You understand that spontaneous adverse event reporting, such as your department collects and analyzes, has been demonstrated to substantially underquantify the real complications in the world?
> A: So the adverse events that are reported to us, complications, complaints that are reported to us, are a subset of the events, complaints, complications that occur in the field.[266]

In fact, Ethicon employees ensured that they would not "actively" collect any complaints. When discussing how to perform a marketing survey with a number of physicians Dan Smith, the Lead of the TVT-O project, wanted ensure Ethicon people did not ask physicians questions that might "collect" a complaint:

> Just a thought with regard to us collecting information. Paul, what was the ruling from our compliance group regarding us asking questions/collecting data, did we have to log issues as complaints????" et cetera. If so, we should do this in a manner that avoids this issue.[267]

Dr. David Robinson, Ethicon's Medical Director, noted a reason that Ethicon might not want to actively collect adverse events about its products: "[I]f this starts getting reported, it is going to scare the daylights out of docs."[268]

Even though Ethicon limited its "surveillance" to passively collecting complaints, it did not do this well. For example, Mark Yale, the head of Ethicon's Worldwide Customer Quality

[266] Lamont Dep. (4/4/13) 389:25-390:23; Yale Dep. (8/7/13) 126:20-127:7 ("So you would agree that generally in a passive complaint collection, which is what Ethicon had prior to this discussion about the registry, for example, in a passive collection, that it is well known and well recognized that adverse events are underreported. Correct? THE WITNESS: In general, the basic understanding in the world of complaints and adverse events is that you do not get 100 percent reporting, that, you know, it is not the perfect collection model to gather. So, yes, they are, in some manner, underreported.").
[267] ETH.MESH.01811770.
[268] ETH.MESH.00756984 (Email from David Robinson, M.D. to Giselle Bonet and Marty Weisberg).

team testified that all Ethicon employees had a legal duty to report any and all complaints to the Company about which they became aware.[269] When shown documentation, Yale admitted that this collection system was flawed. For example, employees in a US call center failed to report complaints,[270] employees in Eastern Europe did not know they were required to inform the Company of complaints and adverse events,[271] one Portugese employee testified that he would not have reported the complaint, but someone had already informed the regulatory authorities:

> Q. So Francisco in Portugal working for Johnson & Johnson Medical says he wouldn't have reported this to you, this complication, except for the fact that somebody reported it to their regulatory authorities. Right?
> A. That's what he wrote. Correct.[272]

This line of questioning led to a consistent theme about adverse events and complications tracking at Ethicon – you don't know what you don't know. Yale testified:

> Q. So as you sit here today, you have no idea how many other complaints didn't make it here from Portugal, because Francisco Noronha from Johnson & Johnson decided that if it wasn't reported to his regulatory agency, he's not going to tell you about it. Right?
> THE WITNESS: I don't know what I don't know.[273]

When David Menneret, an employee of the mesh manufacturer at Ethicon SARL received a complaint about mesh being frayed (a significant issue as discussed above) he was unsure whether to report it as a "complaint" into the Ethicon complaint tracking system. He wrote:

> Please see attached below a letter...regarding Mesh fraying. I don't know exactly who should be informed of this kind of customer feeling so feel free to forward to anyone concerned. Do you think this should be entered as a complaint in the system?[274]

[269] Yale Dep. (8-7-2013) 140:12 to 140:16.
[270] Yale Dep. (8-7-2013) 145:12 to 145:15.
[271] Yale Dep. (8-7-2013) 155:21 to 155:25.
[272] Yale Dep. (8-7-2013) 159:5 to 159:10.
[273] Yale Dep. (8-7-2013) 160:16 to 160:24.
[274] ETH.MESH.01814252.

Again, Yale testified that he could not know how many complaints went to the manufacturer about the fraying from the manufacturing process that ultimately were not reported to Ethicon's complaint tracking system. He testified as follows:

> Q. You don't know how many times Menneret didn't report a complaint either. Right? You don't know what you don't know. Right?
> THE WITNESS: As I said before, I do not know what I do not know….[275]

Prior to March of 2006, Ethicon did not even have a formal procedure in place to capture adverse events from its own clinical trials. Therefore, it had no idea how many adverse events occurred but were not reported from those trials.[276]

In addition to Ethicon's inability to appropriately capture complaint data, Ethicon's reporting of that data to physicians and patients was misleading. As noted above, the patient brochures failed to report the frequency and severity of injuries seen with TVT-O procedures. For example, none of the brochures disclose that more than one in four women will experience leg/thigh/groin or nerve pain from a TVT-O procedure. When quoting numerous studies as evidence of safety, Ethicon failed to inform patients and physicians that the investigators of one study felt it was unethical to continue the TVT-O arm because of the leg/thigh/groin/nerve pain being inflicted on patients in that arm of the trial.[277]

In addition to the marketing materials, Ethicon also provided physicians with "Complications Statements" during training or upon request. These "Complication Statements" relied upon the information captured in Ethicon's complaint system – the same system described above. Accordingly, the capture of information for these statements was already severely compromised. However, even for those events Ethicon did capture, the reporting of these events

[275] Yale Dep. (8-7-2013) 168:24 to 169:12.
[276] Yale Dep. (8-7-2013) 194:22 to 195:7.
[277] Teo, *supra*, n. 128

in the Complications Statements was completely misleading.

Joseph Scavona, a complaint analyst, was responsible for creating one of these Complications Statements that was provided to physicians. He described how he created the statement and how, if a woman had multiple injuries, he only listed one injury on the chart. He wrote:

> [S]ome complaints could be described with multiple main & sub categories, but each complaint was only labeled with one of these categories (e.g. patient had pain, bleeding, hematoma, exposure, and dyspareunia thus complaint was coded only "mesh exposure").[278]

This completely misrepresented the actual harms data. Moreover, the person making these decision, Scavona, was not a medical doctor. He recognized these limitations and requested that medical review the complications data, but it did not occur.[279] Instead, physicians were provided with misleading, inaccurate and incomplete information in the Complications Statements.[280]

In my opinion Ethicon's collection and reporting of adverse events and complications to physicians and patients was incomplete, inaccurate and misleading. As manufacturers are the only entities with access to complaint information, physicinas and patients must rely upon them to provide timely, accurate and complete information. Ethicon failed to do so. Without accurate information, physicians could not and cannot obtain informed consent from their patients, nor can patients give informed consent. Ethicon's complaint collecting and reporting system made this impossible.

M. Ethicon did not inform physicians and their patients that Material Safety Data Sheets (MSDSs) for polypropylene resin used to manufacturer polypropylene meshes warned against use of the mesh in a permanently

[278] ETH.MESH.02122904 (Ex. 970) (Email from Joseph Scavona to others re "TVT Complications Statement 2008"). Complications Statement attached at ETH.MESH.00007091 at 2 (Ex. T-970).
[279] *Id.*
[280] Yale Dep. (8-8-2013) 294 to 300.

implanted medical device and that studies show that polypropylene causes sarcomas in laboratory rats.

According to Ethicon Medical Director, Dr. Martin Weisberg, a Material Safety Data Sheet (MSDS) is "a document that discusses the product, the composition, any potential hazards from it . . . Generally, the safety particular of products."[281] As it relates to polypropylene, I have reviewed several MSDSs for polypropylene resin used to manufacturer meshes used in various pelvic floor meshes. All of the MSDSs discussed below are available to the public.

Sunoco, the manufacturer for the polypropylene resin used to manufacture Ethicon's pelvic floor products lists the possibility that polypropylene mesh can cause tumors or cancer. This is documented by the Sunoco MSDS[282] from April 13, 2005 which states in relevant part:

> 15. OTHER INFORMATION
> Follow all MSDS/label precautions even after container is emptied because it may retain product residue.
> COMPONENT TOXICITY: Polypropylene has been tested in laboratory rats by subcutaneous implantation of discs or powder. Local sarcomas were induced at the implantation site. No epidemiological studies or case report suggest any chronic health hazard from long term exposure of polypropylene decomposition products below the irritation level. (OARC, 19, 128).[283]

Dr. Martin Weisberg, Ethicon Medical Director, is not only familiar with this MSDS, he also has personal experience with it. Dr. Weisberg agrees that the manufacturer of Ethicon's mesh did a study by implanting it under the skin of rats and it did in fact induce sarcomas.[284] Dr. Weisberg also agrees "if there was evidence of cancer-causing abilities of polypropylene . . . a reasonable doctor would want to know."[285] And, despite evidence to the contrary in the above MSDS for the resin used to make the polypropylene mesh for TVT, he is not aware of any

[281] Weisberg Dep. (8/9/13) 909:2-9.
[282] ETH.MESH.02026591 at 6591-6595.
[283] *Id.* at 02026595.
[284] Weisberg Dep. (8/9/13) 951:6-10.
[285] *Id.*

instance when Ethicon "disclosed to any doctor that there's any evidence that the use of polypropylene mesh might induce sarcomas in its patients."[286]

Dr. David Robinson, a former Ethicon Medical Director, testified he was unaware of Ethicon ever performing any studies or research to determine whether polypropylene could cause cancer in the long term.[287] In addition, he testified that Ethicon never disclosed "the potential that polypropylene in the product could be cancer causing."[288] Dr. Robinson also testified that it would be reasonable for physicians to want to know about polypropylene possibly causing cancer.[289]

Another MSDS from Chevron Phillips[290], a manufacturer of polypropylene resin states:

> MEDICAL APPLICATION CAUTION: Do not use this Chevron Phillips Chemical Company LP material in medical applications involving permanent implantation in the human body or permanent contact with internal body fluids or tissues.
>
> Do not use this Chevron Phillips Chemical Company LP material in medical applications involving brief or temporary implantation in the human body or contact with internal body fluids or tissues unless the material has been provided directly from Chevron Phillips Chemical Company LP under an agreement which expressly acknowledges the contemplated use.
>
> Chevron Phillips Chemical Company LP makes no representation, promise, express warranty or implied warranty concerning the suitability of this material for use in implantation in the human body or in contact with the internal body fluids or tissues.

With respect to the Chevron Phillips MSDS, Ethicon Medical Director, Dr. Martin Weisberg, testified that he did not have the Chevron Phillips MSDS in 2001 when he reviewed

[286] Id. at 951:11-16.
[287] Robinson Dep. (9/11/13) 1105:17-110:14.
[288] Robinson Dep. (9/11/13) 1114:15-18.
[289] Robinson Dep. (9/11/13), 1115:5-19.
[290] Chevron Materials Safety Data Sheet Marlex Polypropylenes (All Grades) Revision Number: 3 (Ex. T-3137).

the Sunoco MSDS and no one at Ethicon alerted him to it.[291] If he had been alerted to the Chevron Phillips MSDS, it may have "triggered" an investigation on his part.[292] He also believes that if Ethicon knew about this MSDS, Ethicon should have studied the issue and, if they did not do so, it would have been a violation of the company Credo.[293]

Total Petrochemicals, the polypropylene resin manufacturer for the polypropylene used in AMS' pelvic floor products, Technical Data Sheet for Polypropylene PPR 7220, states in bold red lettering "Under no circumstances are any products sold by Total Petrochemicals suitable for human or animal implants." It is further documented that, "The above-mentioned product is NOT in compliance with the US pharmacopoeia because we DID NOT perform required tests." (emphasis from the original document).[294]

The manufacturer of the polypropylene resin for the polypropylene used in competitor pelvic floor products, Phillips Sumika Polypropylene Company, included a similar warning in its MSDS.[295] Specifically, it states:

> Do not use this Phillips Sumika Polypropylene Company material in medical applications involving permanent implantation in the human body or permanent contact with internal body fluids or tissues. Do not use Phillips Sumika Polypropylene Company material in medical applications involving brief or temporary implantation in the human body or contact with internal body fluids or tissues unless the material has been provided directly from Phillips Sumika Polypropylene Company under an agreement which expressly acknowledges the contemplated use. Phillips Sumika Polypropylene Company makes no representation, promise, express warranty or implied warranty concerning the suitability of this material for the use in implantation in the human body or contact with internal body fluids or tissues.

As discussed above, the possibility that polypropylene mesh can cause tumors or cancer

[291] Weisberg Dep. (8/9/13) 944:16-945:5.
[292] *Id.*
[293] *Id.* at 947:4-19.
[294] ETH.MESH.02026591.
[295] Phillips Sumika Polypropylene Company Material Safety Data Sheet Marlex Polypropylene (All Grades) Revision Number: 5.03 Revision Date: 12/4/2008.

is documented in the Sunoco MSDS, the manufacturer of the polypropylene resin used in the TVT Prolene mesh.[296] Specifically, the Sunoco MSDS from April 13, 2005 states: COMPONENT TOXICITY: Polypropylene has been tested in laboratory rats by subcutaneous implantation of discs or powder. Local sarcomas were induced at the implantation site. No epidemiological studies or case report suggest any chronic health hazard from long term exposure of polypropylene decomposition products below the irritation level."[297]

Despite this warning in the MSDS for the polypropylene resin used to manufacture the TVT mesh, there is no evidence that Ethicon informed surgeon about this important information contained in various Manufacturer Safety Data Sheets (MSDS) regarding the use of polypropylene. This information includes the dangers of using polypropylene in a permanent implanted medical device set forth in MSDS that were in the public domain and available to Ethicon if they chose to look. Ethicon also failed to inform physicians that laboratory studies on rats showed that polypropylene caused sarcomas.

The fact that this information has not been disclosed to physicians in any manner (IFUs, direct letters or promotional materials) is especially concerning in light of literature showing reports of cancer associated with polypropylene. Specifically, there have been cases of pseudotumor reported in polypropylene for hernia mesh[298] and inflammatory myofibroplastic tumor of low malignant potential with a TVT device.[299] In addition, there have been 2 cases of bowel cancer associated with mesh used for abdominal sacrocolpopexy, one associated with mersilene and one with polypropylene and TVT placement.[300] A case of primary vaginal

[296] ETH.MESH.02026591-6595.
[297] ETH.MESH.02026595.
[298] Karrem, M., Community Oncology, Volume 7/Number 4/April 2010.
[299] Kwon S., et al, Female Pelvic Med Recontruct Surg, Volume 18, Number 4, July/August 2012.
[300] Ahuja, S., et al, Gynecol Surg 2011, 8:217-221.

leiomyosarcoma associated with TVT and anterior repair with Bard Duraderm has also been reported.[301]

Finally, a report of angiosarcoma associated with Darcon vascular grafts was reported in 1999.[302] The authors of this article noted at least 8 other sarcomas developing at the site of vascular prosthesis, and that the rate of these sarcoma, associated with foreign bodies, was much higher than the rate of sarcomas in general. All sarcomas associated with Dacron grafts were high grade histology and disseminated at the time of presentation. The authors also describe sarcoma reported at the site of other foreign bodies, such as shrapnel, bullets, steel plates and retained surgical sponges. They also note that the latency period from the acquisition of the foreign body and the development of sarcoma had a mean of 33 years. They document that a chronic foreign body reaction, the same "microscopic foreign body reaction" described by Dr. David Robinson in his Sept 2013 deposition as being clinically insignificant, was the etiology of this carcinogenesis. The authors also describe sacromas developing in rodents after inert plastic polymers were placed in their soft tissue: "The sarcomas developed in rodents in which thick fibrous capsules developed around the implanted material." The authors conclude: "For unknown reasons, the cells in this inflammatory and repair process may undergo a malignant transformation, probably associated with oncogene activation and tumor suppressor gene inactivation. Further studies are warranted to search for the mechanisms involved in foreign body tumorgenesis." To date no manufacturer of mesh products has investigated this oncogenic potential as the authors recommended.

In a report from the International Agency for Research on Cancer: Surgical Implants and Other Foreign Bodies, “When several polymers were tested in rats according to the same

[301] Moller, K., et al, Gynecologic Oncology 94 (2004) 840-842.
[302] Ben-Izhak, O., et al, Am J Surg Pathology, Issue: Volume 23 (11), 1999, p. 1418.

experimental protocol, sarcoma incidences ranged from 70% (polypropylene) to 7% (silicone)."[303] "Polymeric implants prepared as thin smooth films (with the exception of poly(glycolic acid)) are POSSIBLY CARGINOGENIC TO HUMANS."[304]

Given the fact that hernia mesh placement increased in the 1990's with the advent of laparoscopic placement, and that vaginal mesh placed for SUI and POP accelerated in the 2000's, we may be on the cusp of an ever increasing number of foreign body tumors associated with vaginal mesh. Ethicon did not undertake any long term testing to determine whether or not these warnings on the polypropylene resin manufacturers MSDS were associated with long term consequences for permanent human use. This is true despite the fact that Ethicon has knowledge of three of these cancer reports (Kwon, Moller and Ahuja) as they are referenced in Ethicon's 2013 Clinical Evaluation Report regarding TVT.[305]

Additionally, there is no evidence that Ethicon made any effort to inform surgeons of important information contained in various Manufacturer Safety Data Sheets (MSDS) regarding the use of polypropylene. This information includes the dangers of using polypropylene in a permanent implanted medical device. And, that laboratory studies on rats showed that polypropylene caused sarcomas in laboratory rats. Clearly, these facts are critical information relevant to both the surgeon evaluating his or her treatment options and to the patient's informed consent decisions. As a result, Ethicon failed to act like a reasonable and prudent medical device manufacturer.

N. Ethicon did not properly inform physicians and their patients that toxicity testing of the polypropylene mesh revealed that it was cytotoxic or toxic to cells.

[303] International Agency for Research on Cancer, Summaries and Evaluations, Vol.:74 (1999).
[304] McGregor, D.B., et al, European Journal of Cancer 36 (2000) 307-313 (emphasis added).
[305] ETH.MESH.10150515.

Cytotoxicity means toxicity to the cells causing cell injury or death.[306] In a May 26, 2000 Ethicon Memo titled "Review of biocompatibility on the tension-free vaginal tape (TVT) system for compliance to FDA,"[307] the review contains a "Cytotoxicity Risk Assessment for the TVT (Ulmsten) Device" from August 8, 1997.[308] The Cytotoxicity Assessment states "there is some evidence to suggest that the PP [polypropylene] mesh from the sterile Ulmsten device may have cytotoxic potential.[309] In addition, ISO Elution testing "resulted in marked cytotoxicity in tests conducted at Ethicon (Scotland)."

According to former Ethicon Medical Director, Dr. David Robinson, Ethicon never performed "a single long-term study . . . to determine whether or not the Ethicon mesh is clinically cytotoxic in women."[310] In addition, in its IFUs and Patient Brochures, Ethicon never informed physicians or their patients about the possibility of cytotoxicity.[311] Dr. Robinson testified that if there is a clinical related outcome related to cytotoxicity, it is reasonable for physicians to want to know that the mesh in the TVT product had been tested multiple times to be severely or marked cytotoxic.[312]

Cytotoxicity can cause death to cells that can lead to an inflammatory response leading to a multitude of injuries, including serious adverse complications such as erosions, chronic pelvic pain, recurrence, worsening incontinence, dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction or the need for additional surgeries.

Ethicon did not undertake any long term testing to determine whether the marked

[306] Robinson Dep. (9/11/13) 1091:11-21.
[307] ETH.MESH.06852118 at 2118-2129 (5/26/2000 Biocompatibility Review).
[308] ETH.MESH.06852120 (8/8/1997 Cytotoxicity Risk Assessment).
[309] *Id.* and Robinson Dep. (9/11/13) 1098:23-1099:9.
[310] Robinson Dep. (9/11/13) 1101:24-1102-5.
[311] Robinson Dep. (9/11/13) 1114:15-18.
[312] Robinson Dep. (9/11/13) 1115:5-19.

cytotoxicty found in the TVT mesh had long term consequences for permanent human use. This is true despite the fact that its own test results showed the mesh to by cytotoxic.

The potential for cytotoxicity or cell death is important information that physicians need to know in order to pass the information on to their patients so that an informed decision can be made about whether to have a permanent medical device implanted in their body. It is clear from Ethicon's Medical Director David Robinson that this information was never passed on to physicians despite the fact that it would have been reasonable for physicians to have this information. As a result, Ethicon did not act as a reasonably prudent medical device manufacturer in it failed to inform physicians and their patients about the risk of its mesh being cytotoxicity.

V. CONCLUSION.

Ethicon has marketed and sold the TVT-O despite the fact that it is contains numerous characteristics that make it unsuitable for implantation in a woman's vagina. These characteristics include the following: (1) degradation of the mesh; (2) chronic foreign body reaction; (3) fraying and particle loss; (4) Infections and Bio-films; (5) roping and curling of the mesh; (6) loss of pore size with tension; (7) fibrotic bridging leading to scar plate formation and mesh encapsulation; and (8) shrinkage/contraction of the encapsulated mesh.

Not only does Ethicon sell a product which should never be put in the vagina, it failed to inform physicians and their patients about numerous risks associated with the product despite the fact that these risks were known before the product was launched. Ethicon has removed the ability of physicians to appropriately inform their patients of the risks and benefits of the TVT-O and made it impossible for women to consent to the procedure. In addition, despite having knowledge to the contrary, Ethicon never informed physicians and their patients that the TVT-O was associated with cancer and could be toxic to their bodies. Finally, while keeping

this information from women, Ethicon marketed its product with promotional pieces that did not disclose key conflict of interest information or the true complication rates of its products.

As a result of these failures as fully set forth in this report, the TVT-O has caused and will continue to cause a multitude of injuries in women, including the possibility of multiple erosions that can occur throughout one's lifetime, chronic and debilitating pelvic pain, nerve injury, recurrence, worsening incontinence, chronic dyspareunia, wound infection, rejection of the mesh, sexual dysfunction, urinary and defecatory dysfunction, vaginal scarring, wound healing problems, injury to ureters, pelvic abscess formation, risk of infection, and/or the need for additional surgeries, among others.

All opinions I have are to a reasonable degree of medical certainty. I understand discovery is still ongoing in this case and I reserve my right to amend my opinions if further information is provided in any form including, but not limited to corporate documents, depositions and the expert reports of both Plaintiff and Defense experts.

I declare under penalty of perjury that the foregoing is true and correct.

This 21 day of February 2014

Bruce Rosenzweig, M.D.